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CLEFT LIP AND PALATE IN TASMANIA.

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THE frequent familial occurrence of congenital clefts of the lip and palate has long been a recognized factor in the ætiology of these anomalies. The mode of inheritance, however, has remained obscure, and a poor basis for answering the invariable questions of much concern to close relatives as well as to those affected by this deformity. Until recent years the incidence of the anomaly in any particular community, and especially the relative frequency of its familial to its spordiac occurrence, has been only roughly estimated.

The chief reason for this has been the lack of reliable facts and statistics in any particular community. A record of clefts of the lip and palate is not generally included in birth registrations, and common minor grades of the deformity are often ignored. It was not until Fogh-Andersen (1942) of Copenhagen was able to study the mass of data resulting from compulsory notification at birth of all such anomalies in the population of Denmark that any real light was shed on these matters. His work and the conclusions therefrom have become the basis of present-day teaching and advice, and so far, no comparable or counterpart opportunity for investigation has presented itself elsewhere. In essence, his conclusions were that harelip with or without associated cleft palate and isolated cleft palate were two different malformations with no genetic connexion, the former more frequent in males, the latter in females. He considered the likely manner of inheritance for harelip and cleft palate to be that of "conditioned dominance" with sex limitation to males, whereas for isolated cleft palate he favoured that of simple dominance with failing manifestation and sex limitation to females. He set out empirical figures of genetic prognosis for different groups of relatives (see Table X).

In Australia we have had no reliable statistical data whatever concerning these anomalies in our community. One of us (B.K.R.), however, who has been Consulting Plastic Surgeon in Tasmania since 1946, has had a unique opportunity for a comprehensive survey of cleft lip and cleft palates in that State, where the large majority of these babies are forgathered for advice and surgical treatment at one particular centre. Because of the importance of this opportunity and of what seemed to be a high local occurrence rate for this condition, appropriate records were accumulated with a view to

some future organized social and genetic study. This paper is an abridged version of the results of that study, made in 1958[1] in conjunction with a geneticist (J.A.T.).

The colourful epic of Tasmania's settlement is well known. The small island's population of 333,000 has grown by continued European migration and steady natural increase from the time of the first settlements of Van Diemen's Land in 1803. Until more recent years, difficulties of travel and the relative isolation of pioneer family groups, like the social barriers separating convicts or ticket-o'leave men from soldiers, administrators and free settlers, have provided conditions for frequent intermarriage among the early population. Better opportunities elsewhere for the more progressive and intellectual have favoured a differential drift of population from the close island community to wider horizons of the Australian mainland. These observations are commonly made to explain to a visitor his impressions of a high incidence of mental retardation and congenital malformation. Scott (1957) states that this migration from outback areas to the cities or the mainland "robbed the rural areas, especially the inhospitable hill country, of much of their able youth, leaving behind the less able, amongst whom in many isolated areas intermarriage has bred a feeble-minded stock".

Bearing in mind this background, but without prejudice, we have carried out our study with certain broad objects in view, namely (*a*) to determine the occurrence rate of cleft lip and palate in this State; (*b*) to see whether the apparent high incidence of these anomalies was real, and whether it had any regional geographic basis or relation to consanguineous marriage; (*c*) to study the genetic basis in relation to Fogh-Andersen's conclusions; (*d*) to establish the case for instituting birth records of such anomalies in this country; (*e*) finally, to question the eugenic wisdom of a full-scale migration programme permitting unchecked admission of families manifesting the trait of cleft lip and palate to an island community which already carried an apparently high incidence of several congenital anomalies.

Materials and Methods of the Present Study.

During the year 1958, the family history of all individuals with cleft lip and/or palate born in Tasmania during the years 1945 to 1957 inclusive was investigated. These numbered 160. Ascertainment of propositi was in most cases made through their attendance at the plastic surgery clinic at the Royal Hobart Hospital. Others were found through reports from private medical practitioners, from hospital case records made for reasons other than the defects considered here and from death certificates. Government medical officers stationed in country areas, who referred many patients to the plastic surgery clinic, provided detailed information on families in their districts, while the cooperation of mainland hospitals ensured that the few affected individuals who had travelled interstate for treatment were not overlooked in the survey.

The results of cross-checking one source with another whenever possible led to the conclusion that ascertainment was virtually complete. All propositi were identified by name, so that there was no possibility of duplicating records.

As Fogh-Andersen (1942) points out, hospital surgical records, which are commonly used, are not suitable for the calculation of birth frequencies of cleft lip and palate, because many of these patients are submitted to multiple operations. Such difficulties were overcome in this study by basing the analysis on the year of birth of the propositus and not on the year of operation.

The family history of each propositus was recorded in detail on standardized *questionnaire* sheets (Thomson, 1959). These included details of the propositus' sibship and other "close" relatives (children, parents, grandparents, siblings' children, parent's siblings, and parent's siblings' children).

During the course of the investigation we travelled the island widely and many domiciliary visits were made, while in other cases details were obtained from parents or guardians interviewed during their attendance at a hospital clinic. Excellent cooperation was obtained from the families involved; in no instance was information refused—nor was reticence in disclosing illegitimacies and adoptions encountered. Whenever possible, family histories were checked with several members of the kindred.

In addition to the 160 propositi born in the period 1945-1957 inclusive, the family histories of 61 propositi who were either born in Tasmania outside the years covered by the study or were recent immigrants to the country have also been investigated. The main propositus material thus consists of an unselected group of cleft lip and palate cases. The additional material collected outside the 1945-1957 group cannot be regarded as unselected. The degree of severity of the defect, interest of the family history or availability for follow-up may have influenced ascertainment and detail of the investigation made. Nevertheless, some supplementary use can be made of these propositi in a study of cleft lip and palate.

Annual figures for the adult population, live births and still-births and the age of mothers at the time of birth of their children were obtained from the official publications of the Commonwealth Statistician.

Sibship records are not available for all the propositi. In five cases the family had moved overseas and could not be traced; nine subjects were not traced despite a considerable search within Tasmania; two subjects had been adopted without their guardians' learning anything of other members of the family; while for five of the nine propositi who had died for various reasons (one from malnutrition, two from pneumonia, one from "respiratory failure" (subarachnoid hæmorrhage disclosed at autopsy), one from an unknown cause, one from drowning and three others from accidents), complete records of the sibships were also not obtained.

Owing to the impossibility of recording all still-births in the families involved, these have normally been recorded for the propositus' sibships only.

The propositi forming the unselected series in this work have been divided into two groups according to whether a demonstrable "familial disposition" to the trait is or is not apparent in the kindred concerned.

Familial disposition is of necessity a rather indefinite concept arising from the long recognized fact that . . . "few malformations behave as clear-cut hereditary traits, even though heredity seems to influence the development of many of them" (Anderson and Reed, 1954). It is particularly noticeable in the case of cleft lip and palate that affected relatives are often only distantly related to the propositus (that is, are not "close" relatives—see above); but they should not be ignored. However, in evaluating the importance of hereditary factors, as there is an overall incidence of 1:600 amongst births in the Tasmanian community, more than one affected individual may appear quite by chance in large kindreds. An estimate of familial tendency is in error from two main sources, as follows.

1. The finding of affected members of a kindred depends on the amount of information available about any family, on the number actually in the sibships, and on the number of relatives about whom the interviewed individuals have any knowledge. The majority of families involved in our study have in fact been resident in Tasmania for three generations, but some were more recent immigrants and often had even close relatives interstate or overseas about whom they knew little or nothing.

2. There is obviously no way of distinguishing between coincidental sporadic cases appearing together in one genealogy, and genetically controlled familial occurrences. When the latter are at best rather few, and the defect is common in the population at large, the error in estimates of familial tendency from this source is likely

[1] Under the sponsorship of the National Health and Medical Research Council.

to become serious. It is certainly not satisfactory to limit the idea of familial tendency to instances in which defects of the same type occur in the pedigree more than once, as was done by Fogh-Andersen (1942) when working with cleft lip and palate. This would presuppose that we have a knowledge of the genetic relationship between cleft lip and cleft palate, and cleft palate by itself, in all cases, and that there is no connexion between them. Such a procedure leads, of necessity, to a failure to obtain evidence on the question of whether the two defects are always unrelated, or whether they overlap genetically in some kindreds.

Affected individuals other than the propositus were encountered amongst the relatives of 52 (32·5%) of the 160 propositi comprising the unselected series of cases. The affected relative was "closely related" (see above) to the propositus in 32 (23·1%) instances.

Incidence of Cleft Lip and Palate in Tasmania.

During the study period (1945-1957 inclusive), 160 children with harelip and/or cleft palate were born amongst 96,510 live births in Tasmania (1·66 per thousand live births). In comparison with reports from other countries, this represents a high incidence of the anomaly.

A number of subjects examined during the course of the present survey were children born between 1945 and and 1957 to parents who have since migrated to Tasmania. Such cases have not, of course, been included in the series described here, and necessarily constitute an incomplete record, in view of the fact that many such defects would be corrected in the country of origin, and attention would be drawn to them only if they were of a type necessitating secondary operation. Nevertheless, it is interesting to note that three Dutch, two English, one Polish and one Sinhalese family were thus encountered during the investigation. The high incidence of cleft lip and palate amongst certain migrant nationalities makes the collection of information for the Tasmanian population desirable. This might be related in later studies to changes in gene frequency resulting from the extensive migration programme which has been in operation since the end of World War II.

There are no significant differences in the incidence of harelip and cleft palate in the various districts within the State recognized by the Commonwealth Statistician (Table I). The occurrence of these anomalies appears to follow the population distribution closely, except in the north-east, where the incidence of cleft defects reaches a maximum (Table I), and where there is also an unusually high proportion of school-children of low intellectual ability as shown by the recent survey carried out by Scott (1957). No consanguinity was encountered amongst the parents of the propositi of the present study. In several instances, however, the propositus' grandparents on one side were related, and this may have contributed to the pattern of frequency of these abnormalities seen in Tasmania today.

No significant difference in the frequency of cleft malformations was observed when rural and urban populations were compared (Table I), a finding in accord with that of Fogh-Andersen (1942) and of Phair (1947). Contrary to the opinion of the former, both investigators in the present survey considered that the great majority of the propositi came from families of low standing—an impression confirmed in both city and country during the numerous domiciliary visits carried out.

In Denmark, the incidence of harelip and cleft palate observed by Fogh-Andersen (1942) was 1·45 per thousand live births—a figure which is only a little higher than that quoted by MacMahon and McKeown (1953) for Birmingham, England, and by Ivy (1951), by Phair (1947) and by Grace (1943) for American populations.

The incidence of these defects in Tasmania is not significantly greater than in Denmark (Deviation/S.E. = 1·2) but is significantly higher (Deviation/S.E. = 2·45) than in Birmingham (MacMahon and McKeown, *loco citato*), even though the latter figures were calculated for total rather than live births and are therefore probably maximum estimates (compare Fogh-Andersen, 1942). Similarly, the incidence calculated for American populations by Grace, Ivy and Phair, and that calculated for Canada by Hixon (1951), are significantly lower than those reported here. Much must depend on the accuracy of the survey in investigations of this nature, and a diversity of techniques have been employed in these studies, so that undue emphasis should not be placed on the statistical significance of such differences. Nevertheless, the fact remains that the incidence in Tasmania of cleft lip and palate defects is the highest yet observed in a population of dominantly Caucasoid ancestry.

Classification of Cleft Defects.

We have used the common current surgical classification. This is set out as follows.

Group I: clefts of the lip only (prealveolar clefts). These may be either unilateral or bilateral, and with variation in degree from a slight notch in the upper lip to a complete cleft into the nostril. In the complete forms of isolated cleft lip the alveolus as far as the incisive foramen may be involved. Group I cases are subdivided as follows: lip cleft on left side, I. (1). L; lip cleft on right side, I. (1). R; bilateral cleft lip, I. 3.

TABLE I.

Geographical Distribution of Cleft Lip and Palate Cases, 1945 to 1957.

Material.	Hobart and Suburbs.	Launceston and Suburbs.	Urban.	North-Western.	North-Eastern.	North-Midland.	Midland.	South-Eastern.	Southern.	Western.	Rural.	Total.
Live births	27,972	13,716	41,688	22,967	7493	3275	4210	3704	9870	3303	54,822	96,510
Observed Group I and III cases	37	15	52	26	11	1	3	1	10	2	54	106
Expected group I and III cases	30·72	15·06	45·78	25·22	8·23	3·60	4·62	4·07	10·84	3·63	60·21	105·99
	By districts $\chi^2_8 = 7·82$.[1] Rural versus urban $\chi^2_1 = 1·49$[1].											
Observed Group II cases ..	13	12	25	13	7	3	2	1	1	1	28	53
Expected Group II cases ..	15·36	7·53	22·89	12·61	4·11	1·80	2·31	2·03	5·24	1·81	30·11	53·00
	By districts $\chi^2_8 = 10·77$.[1] Rural versus urban $\chi^2_1 = 0·34$.[1]											
Total cases observed ..	50	27	77	39	18	4	5	2	11	3	82	159
Expected	46·09	22·60	68·69	37·84	12·34	5·40	6·94	6·10	16·26	5·44	90·33	159·02
	By districts $\chi^2_8 = 10·28$.[1] Rural versus urban $\chi^2_1 = 1·77$.[1]											

[1] Not significant at 5% probability level.

Group II: cleft of the palate only (post-alveolar clefts). These may involve both the hard and soft palate or the soft palate alone. A minor form is that in which the uvula is split, but the palate is otherwise normal.

Group III: complete clefts involving both lip and palate. These constitute the most severe forms of the malformation, especially when bilateral in manifestation. Cases are again designated according to the side of the lip involvement as follows: cleft lip and palate on the left side, III. (1). L; cleft lip and palate on right side, III. (1). R; bilateral cleft lip with cleft palate, III. 3.

Some authors have recognized other sub-types of cleft, depending on the degree of the condition and on the presence or absence of intact bridges of soft tissue (Fogh-Andersen, 1942). Such distinctions lead to many difficulties, as in survey work the diagnosis must often be made post-operatively, from hospital records varied in detail, or even from statements made by relatives.

Unilateral clefts of Groups I and III are more common than bilateral defects, and comprise some 77·55% of the clefts of Groups I and III. The predominance of unilateral clefts is more marked in the case of harelip (92% unilateral) than for harelip with cleft palate (73·12%), a finding in agreement with previous investigations. Unilateral clefts of the lip are three times more common on the left than or the right side, while the more severe clefts involving both the lip and palate are twice as frequent on the left as on the right side. This is a significant difference for which we have no explanation.

The frequency of the Group I, II and III type defects in the unselected survey material of the present study agrees very well with that observed amongst the 221 total cases (that is, including the supplementary material, Table II); possible selection of the supplementary material for type of defect was therefore negligible.

The distribution of cases by defect type differs significantly (Thomson, 1959) from that reported by overseas workers. In each instance there are relatively more Group II cases in the Tasmanian series. The corresponding figures for representative surveys are shown in Table III.

Sex Differences in Incidence of Cleft Types.

It has long been considered that cleft lip with or without cleft palate affects more males than females, whereas the sex ratio for cleft palate is about 0·5 (Fogh-Andersen, *loco citato*). In Tasmania, the sex ratio for cleft palate alone is 0·76. The deviation from the expected 1:1 distribution is here not significant ($\chi^2_1 = 1{\cdot}35$, $P = 0{\cdot}10 - 0{\cdot}50$); but the sample is admittedly small.

The sex distribution of lip and palate clefts found in Tasmania has been summarized and further analysed in Table IV, in which comparison with the results of other investigators are made. It can be seen from this table that the sex distribution of all defects as found in the present study is in accordance with that observed by Fogh-Andersen in Denmark, but that there are more males with harelip alone than in Fraser and Baxter's (1954) American material.

Mode of Inheritance.

If a trait is rare in the population and the manifestation probability is low for the genetic systems concerned, it is often extremely difficult to decide to what extent the character involved is hereditarily determined. Further difficulties are encountered as the number of genes concerned becomes greater, until a situation is reached where no direct evidence for the inherited nature of the defect may be obtainable.

The conclusion that harelip and cleft palate are, at least to some extent, genetically determined is supported by data from a number of sources: (i) Identical twin pairs are more often concordant than discordant with respect to these anomalies (Fogh-Andersen, 1942), whereas dizygotic pairs are more often discordant. (ii) The incidence of defectives amongst relatives of propositi is increased as compared with the general population (Table V). A statistical analysis of these figures appears in Table VI. (iii) Although far from conclusive in itself, the fact that there is a difference in sex incidence supports the idea of some measure of genetic control, even if indirect, rather than of some purely mechanical ætiology. The very early critical period for these defects reduces the likelihood that direct sex-hormonal influences are important *per se*. (iv) The resemblance of cleft type amongst affected members of a kindred, seen for Group II and III propositi in Table IV, indicates that the expression of the defects is susceptible to modifying genetic influences, acting directly or indirectly, common to the members of that kindred. Alternatively, it is possible that separate genetic systems are involved in the production of each phenotype; but other evidence indicates that only two systems need be postulated. (v) The frequency of occurrence of cleft lip and palate abnormalities appears to be characteristic for each racial group, and controlled only secondarily, if at all, by environmental conditions (see above). (vi) Comparison with studies made on laboratory animals indicates that close similarities exist in the mechanisms involved in cleft production (Reed, 1956). In mice, the genetic control of lip and palate defects has been conclusively

TABLE II.

Analysis of Clefts Encountered in 160 Propositi Born during the Period 1945 to 1957 Inclusive, Together with Additional Information from 61 Other Cases.

Malformation.	1945–1947 Cases.				Percentage of All 1945–1957 Cases.	Supplementary Cases: Sex.		All Cases.	
	Sex.		Familial Disposition.						
	Male.	Female.	Number.	Percentage Familial.		Male.	Female.	Total.	Percentage of All Cases.
Hare-lip:									
I (1) L.	16	8	6	25·0	15·00	6	4	34	15·38
I (1) R.	8	2	2	20·0	6·25	2	—	12	5·34
I 3	—	4	1	25·0	2·50	—	—	4	1·81
	24	14	9	23·7	23·75±3·37	8	4	50	22·62±2·82
Cleft palate:									
II	24	29	12	22·6	33·13±3·72	8	13	74	33·48±3·17
Hare-lip and cleft palate:									
III (1) L.	22	12	12	35·3	21·25	10	4	48	21·71
III (1) R.	15	1	10	62·5	10·00	4	—	20	9·05
III 3	14	4	8	44·4	11·25	5	2	25	11·31
Side unknown	1	—	1	—	0·63	3	—	4	1·81
	52	17	31	44·9	43·13±3·92	22	6	97	43·89±3·34
Total	100	60	52	32·5	—	38	23	221	—

demonstrated (Reed, 1936, and many later workers, for example, Fitch, 1957).

The discovery that at least two genetic systems are involved in the production of cleft lip and palate in man is usually attributed to Fogh-Andersen (1942); the suggestion was, in fact, originally made by Vaughan (1940), although it remained unverified until Fogh-Andersen's work. Present-day treatments of the subject distinguish sharply between cleft lip with or without cleft palate, and cleft palate occurring by itself. The pattern of inheritance, the sex incidence and the presumed embryological history of the defects all tend to support such a conclusion.

TABLE III.

Survey.	Percentage of All Defects.		
	Group I.	Group II.	Group III.
Beder *et alii* (1956), U.S.A. (white) ..	14	27	59
Ivy (1951) (white)	30	24	46
Fogh-Andersen (1942), Denmark ..	22	20	58
Present survey, Tasmania	23	33	44

Other congenital malformations often accompany clefts of the lip and palate (Thomson, 1959) in the Tasmanian series of cases. Of the 53 propositi with cleft palate alone, 16 (30·2%) have at least one other congenital defect, notably mental disability (13·2%). Only one of the 38 (2·6%) propositi belonging to Group I suffers from any other anomaly. This case involves multiple facial defects, presumably occasioned by a more generalized disturbance of visceral arch development than that normally associated with cleft lip in its hereditary form. Group III propositi have other deformities in five cases out of 69 (7·2%), of which one case only (1·4%) involved mental disturbances. The relationship of these conditions to other defects is thus very different; cleft palate alone is often accompanied by other congenital anomalies, especially by imbecility.

Differences in the incidence of other congenital malformations amongst the relatives of propositi of the three groups are not marked (Thomson, *loco citato*). No figures suitable for comparison with these are available for the Tasmanian population as a whole.

Genetic independence of any of the cleft types should be indicated, as Fogh-Andersen pointed out, by the failure of other types of the deformity to appear in more than chance proportions amongst the close relatives of the propositi of that group (Table VII). Although the Tasmanian material is small, it may be seen that cleft lip with cleft palate and cleft palate alone are genetically related; within Groups I and III, cleft types alternate freely (except for the similarities of cleft type within kindreds occasioned by the genetic background common to members of that genealogy), and no differences from the proportions of cleft types encountered in the population as a whole can be demonstrated. In certain pedigrees, then, cleft palate must be produced by the same genetic system as cleft lip and/or cleft palate. When the Group II cases are analysed, it is found that cleft palate alone is five times more frequent amongst the propositus' relatives than in the general population. Propositi of this group, however, have significantly more affected relatives of their own group than would be expected on the basis of this overall distribution, while the frequency of relatives suffering from Groups I and III types is low enough to be accounted for by chance. Confirmation is thus obtained of the existence of separate genetic systems controlling the formation of cleft lip with or without cleft palate and of cleft palate occurring alone. The two conditions are not, as noted above, entirely independent in all cases; some cleft palates are due to the "lip and

TABLE IV.

Sex Distribution of Lip and Palate Clefts.

Group.	Male.	Female.	Total.	χ^2_1.
Group I:				
Observed in Tasmania ..	32	18	50	—
Expected	—	—	—	—
Fogh-Andersen	32·60	17·40	50·00	0·03
Ivy	35·00	15·00	50·00	0·76
Fraser and Baxter ..	21·43	28·57	50·00	9·12[1]
Group II:				
Observed in Tasmania ..	32	42	74	—
Expected	—	—	—	—
Fogh-Andersen	25·09	48·91	74·00	2·88
Ivy	28·12	45·88	74·00	0·86
Fraser and Baxter ..	32·37	41·62	73·99	0·01
Group III:				
Observed in Tasmania ..	74	23	97	—
Expected	—	—	—	—
Fogh-Andersen	69·26	27·74	97·00	1·13
Ivy	62·08	34·92	97·00	6·36[2]
Fraser and Baxter ..	64·09	32·91	97·00	4·51[2]

[1] Significant at 1% probability level.

[2] Significant at 5% probability level.

TABLE V.

Distribution of Defective Individuals Amongst Relatives of Propositi.

Propositus Group.	Group.[1]	Parents.	Grand-parents.	Siblings.	Sibling's Children.	Parent's Siblings.	Parent's Sibling's Children.	Distant Relatives.	Total Close Relatives.	Total Defectives Amongst Close Relatives.
I	I	—	1	—	—	—	2	3	—	3
	II	—	—	—	—	2	1	1	—	3
	III	—	—	—	—	—	—	1	—	0
	Total 38 ..	72	143	84	7	221	386	—	913	6
II	I	1	1	—	—	—	1	1	—	3
	II	3	—	1	—	3	3	—	—	10
	III	—	—	—	—	—	1	3	—	1
	Total 54 ..	96	166	106	1	329	674	—	1372	14
III	I	—	—	—	—	2	1	10	—	3
	II	—	—	1	—	1	2	5	—	4
	III	1	—	4	—	3	2	7	—	10
	Total 63 ..	120	222	153	0	427	748	—	167	17

[1] Each kindred used once only in each section, even where ascertained through several different propositi

palate" complex, others to the "cleft palate" system. Further evidence bearing on this point is obtained from the pedigree material (presented in full elsewhere; Thomson, 1959), in which Group II defectives occur in the same genealogy as Group I and/or Group III sufferers in 16 (Figure I) of the 47 kindreds (33·0%)—a frequency which is unlikely to be due solely to chance in an unselected series of cases. In this respect, the Tasmanian material differs strikingly from that of Fogh-Andersen, who was unable to demonstrate conclusively the existence of such an interrelationship.

TABLE VI.
Analysis of Incidence of Defect Types Almost Relatives of Propositi.

Defectives.	Defect Type.		
	Group I.	Group II.	Group III.
Observed number of defectives amongst close relatives ..	6	14	17
Expected number of defectives calculated for general population figures (all groups included)	1·51	2·28	2·77
Deviation / S.E.	2·37[1]	4·02[2]	4·54[2]

[1] Significant at 5% probability level.
[2] Significant at 1% probability level.

At the same time, however, it is clear that two different genetic systems are involved. The pattern of sex incidence, association with other malformations, mode of action during development and alternation within kindreds of certain cleft types but not others, confirm this conclusion.

TABLE VII.
Incidence of Cleft Types Amongst Relatives of Propositi.

Propositus Group.	Group of Affected Relative.	Close Relatives Affected.	Total Checked.	Expected Distribution of Affected (Table II).	χ^2_2.
Harelip: I	I	3	—	1·35	—
	II	3	—	2·01	—
	III	0	—	2·63	—
		6	913	5·99	4·77
Cleft palate: II	I	3	—	3·16	—
	II	10	—	4·69	—
	III	1	—	6·14	—
		14	1372	13·99	10·32[1]
Harelip and cleft palate: III	I	3	—	3·85	—
	II	4	—	5·69	—
	III	10	—	7·46	—
		17	1670	17·00	1·55

[1] Significant at 0·1% probability level.

Cleft Lip With or Without Cleft Palate.

Many different genetic mechanisms have been implicated by the workers of the last thirty years; but from the Tasmanian series it is not possible to give any uniform genetic explanation for the patterns of inheritance of harelip with or without cleft palate. Neither a sex-linked dominant nor a sex-linked recessive alone could produce the patterns of inheritance seen in the families studied in Tasmania. Except for two of the kindreds, inheritance is through one side of the family only. These two instances of appearance of the defect in both maternal and paternal lines may well be due to chance in the case of an anomaly as common in the general population as cleft lip and palate. No consanguineous marriages were encountered amongst the parents of the propositi. The typically unilateral transmission of the defect is suggestive of dominant inheritance; the absence of consanguinity would be confirmatory only if the defect was much more rare than is the case in Tasmania—that is, if the frequency in the population was less than one in 1000 births (Jacob, 1911). Valid confirmatory evidence of the dominant nature of the defect was obtained by Fraser (1956), when he found no increase in the frequency of the deformity amongst the other offspring of consanguineous parents with affected children.

Preliminary examination of the Tasmanian material according to the method used by Csik and Mather (1938), and later Mather and Philip (1940), suggested that a partially sex-linked gene or genes might be involved in the inheritance of harelip and cleft palate, a possibility originally arising from a study by these authors of data collected by Schroeder (1931). Participation of partially sex-linked genes would result in the appearance of more affected females than males amongst the siblings of affected females. More affected males than females, on the other hand, would appear in the sibships of affected males.

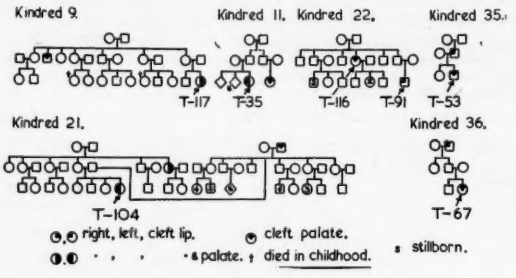

FIGURE I.
Six selected pedigrees illustrating the occurrence in the same family of cleft lip with or without cleft palate and of cleft palate alone.

Further examination of the present pedigree series fails to substantiate the suggestion of partial sex linkage. Unlike Schroeder's material, the Tasmanian series is homogeneous with respect to linkage. This finding further discounts the theory put forward by Fortuyn (1935) that a sex-linked recessive is involved together with an autosomal (not sex-linked) recessive.

Sibships in which one member has cleft lip with or without cleft palate show the expected sex ratio of 1·0 (99 : 82; $\chi^2_1 = 1·6$).

The participation of autosomal recessive genes in the inheritance of harelip and cleft palate is unlikely, as was pointed out by Hogben (1932), because a high proportion of matings of an affected with a normal individual produce defective offspring—a fact which Fogh-Andersen (1956) appears to have neglected when asserting that cleft lip associated with cleft palate is "mostly of a recessive character".

Monogenic Autosomal Recessive Inheritance.

Monogenic autosomal recessive inheritance appears unlikely to account for the observed distribution of cleft cases in the Tasmanian series. If corrections are applied for missed sibships, it is seen that the proportion of affected individuals found in those sibships of the pedigree material which had two normal parents and at least one affected member differs significantly from the expected fraction of 1/4. Such a test is not, of course, affected by the frequency of the trait in the population as a whole, but is based on the assumption of complete penetrance. Fogh-Andersen's (1942) unselected twin series indicates that manifestation probability may be of the order of 67% for harelip with or without cleft palate. It is clear that if a suitable correction factor is applied to compensate for the known failure of manifestation, it would become possible to reconcile the observed and expected figures. Other evidence, as was mentioned above, does not support an explanation based on segregation of one autosomal recessive gene.

Digenic Autosomal Recessive Inheritance.

Digenic autosomal recessive inheritance results in a tendency for a character so determined (unless it is very rare) to appear in more than one member of paternities with two phenotypically normal parents (Hogben, 1932). Hogben has shown that when the two alleles concerned have equal frequencies and there is an incidence of the character of 1:625 in the population at large, the proportion of families of this type having two affected offspring is 9%. Six of 36 relevant sibships with two or more members in the Tasmanian kindreds contain two defectives. This proportion of 16·7% is higher than the expectation of 9%, especially if allowance is made for the reduced manifestation probability of the genetic system involved. Although the figures available are so small that alone they would be of little significance, the frequency of sibships with one affected parent and at least one affected child (two of eight sibships—25%) amongst the Tasmanian families is higher than that expected for digenic autosomal recessive inheritance. Under these circumstances the frequency of such sibships would be expected to decline with the square root of the frequency of the trait (Hogben, *loco citato*).

Simple Autosomal Dominant Inheritance.

Simple autosomal dominant inheritance of harelip and cleft palate cannot be entirely eliminated as a possibility, but would involve the assumption that the penetrance of the gene concerned is very low (less than 67% as estimated from Fogh-Andersen's twin series, mentioned above), and is variable from kindred to kindred.

Digenic Complementary Dominant Inheritance.

Digenic complementary dominant inheritance without linkage was considered by Hogben (1932) to account for the hereditary pattern of harelip and cleft palate. Although correction for lowered manifestation probability results in good agreement of the observed with the expected (1/4) proportions of affected in their sibships, the unequal frequency of matings of the types normal with normal and affected with normal amongst the parents of the affected individuals is contrary to expectation (Hogben, *loco citato*) when the two dominant alleles are postulated to have equal frequencies.

Cleft Palate Without Lip Involvement.

There can be no doubt that the pedigrees of cleft palate, when this occurs by itself, reflect a dominant mode of inheritance, although this is complicated by the apparent reduction of penetrance. In all cases the defect is transmitted through one side of the family only, and there is no evidence of consanguinity in any of the kindreds.

Despite the unequal sex incidence noted earlier, there is no suggestion of sex-linkage when the incidence of the defect amongst siblings of affected individuals is examined (Thomson, 1959).

The unselected twin series compiled by Fogh-Andersen indicates that for cleft palate manifestation probability is again reduced; but no satisfactory numerical estimate can be made from this material. In order to account for the observed departure from expected proportions, a manifestation probability for two complementary dominant genes of 70% to 75%, and for a single dominant gene of about 55%, must be postulated. Neither figure appears unreasonable in the light of the other evidence available. Further difficulties are occasioned by the possibilities that several different genetic systems may be involved, that some cases of cleft palate may be due to the "cleft lip and palate" gene complex and that a high proportion may possibly have exogenous causes.

MATERNAL AGE AS AN ÆTIOLOGICAL FACTOR.

Much attention has been given to the possible significance of maternal age in the ætiology of clefts of the lip and palate. Murphy (1942) and Phair (1947) both supported the contention that maternal age is important, but Fogh-Andersen (1942) and Grace (1943) failed to find evidence of any relation between maternal age and frequency of production of defective children. Reed (1956) considers that such an effect exists in man and experimental animals.

MacMahon and McKeown (1953), in a careful study based on data collected in Birmingham, found no evidence of either a maternal age or birth rank factor for cleft palate alone; but there was evidence of the importance of the former in the case of cleft lip and palate.

The information available in the present study comprises the ages of mothers at the time of birth of their affected children, together with the maternal age distribution of all children born in Tasmania in the years 1949 to 1956 inclusive (Table VIII).

The difference between the mean maternal ages at birth of normal and defective children (total figures, footnote to Table VIII) is just significant at the 5% probability level (difference between means 1·10 ± 0·553). The differences between the mean maternal ages at birth of normal children and Group I and III defectives, and of normal children and Group II defectives, are not statistically significant. There is also no significant difference in mean age of mothers of cleft lip and palate defectives when those families with a demonstrable familial disposition to the trait are compared with others (Thomson, 1959).

Confirmatory evidence of the maternal age effect is obtained from the birth rank data of Table IX, in which a significant excess (1% probability level) of the affected occur in the later birth ranks ($\chi^2_6 = 19{\cdot}85$). There is a notable deficiency of defectives in the lowest birth ranks,

TABLE VIII.

Distribution of Births by Maternal Age.[1]

Incidence of defects.	Maternal Age (Years).						
	15 to 19.	20 to 24.	25 to 29.	30 to 34.	35 to 39.	40 to 44.	45 to 49.
Cleft lip and palate. No family history	4	11	15	13	7	2	—
Cleft lip and palate. Family history ..	1	12	9	7	6	2	—
Total cleft lip and palate	5	23	24	20	13	4	—
Cleft palate	1	7	15	4	7	—	—
Total defective	6	30	39	24	20	4	—
Total Tasmanian births, 1949 to 1956 ..	3979	16,120	16,187	10,627	5517	1657	122[2]

[1] Analysis of maternal age effect:

	Mean age of mothers at birth of children (years).
Defect: Cleft lip and/or palate	26·382±0·552
Tasmanian population (1949 to 1956) ..	25·280±0·026

[2] Based on figures compiled by the Commonwealth Statistician.

TABLE IX.

Analysis of Influence of Birth Order on Incidence of Clefts of the Lip and Palate.

Size of Family.	Birth Order of Propositi.[1]								Total.	Number Expected in Each Birth Position.
	1	2	3	4	5	6	7 to 14	15		
2	9	20							29	14·50
3	8	12	12						32	10·66
4	4	6	6	9					25	6·25
5	—	—	1	3	5				9	1·8
6	—	2	1	—	1	5			9	1·5
7	—	—	—	—	3	1	—		4	0·57
8	—	—	—	—	1	—	—		1	0·125
9	—	1	1	1	—	—	—		3	0·33
10 to 14 ..	—	—	—	—	—	—	—		—	
15	—	—	—	—	—	—	—	1	1	0·06
Observed totals	21	41	21	13	10	6		1	113	
Expected totals	35·80	35·80	21·30	10·64	4·39	2·59		2·36[2]		

[1] Eleven one-child sibships have been omitted.

[2] Birth orders 7 to 15 pooled.

a feature which may be correlated with a decrease in frequency of defective children thought by some authors (Reed, 1956; Murphy, 1942, for congenital malformations in general) to occur amongst births to mothers of the 20 to 24 years age group.

GENETIC COUNSELLING.

Information given to patients and their relations who are concerned by the cleft lip and palate deformity in their family should be based on a careful study of each particular family history, in an attempt to distinguish between those cases which may be primarily of genetic origin and those of a sporadic nature. In the absence of a universally applicable genetic theory, and especially where manifestation probability is reduced, advice must be based on empirical risk tables calculated from a population sample; such figures for the Tasmanian population are given in Table X together with those calculated by Fogh-Andersen (1942) for Denmark. It would, however, be interesting to have such frequencies from other parts of the Commonwealth.

TABLE X.

Maximum Empirical Risk Figures for Cleft Lip and Palate Malformations where an Hereditary Disposition to the Anomaly is Indicated.

Frequency.	Denmark.		Tasmania.	
	Number.	Percentage Risk.	Number.	Percentage Risk.
Frequency in population at birth	—	0·11	—	0·165
Frequency amongst siblings, when one is affected ..	51 : 1106	4·4	9 : 152	5·6
Frequency amongst children when one parent is affected	8 : 224	3·4[1]	7 : 31	18·4

[1] Fogh-Andersen eliminated from consideration the families of certain close relatives of propositi, so tending to select families which had escaped separate detection in his survey because of the few individuals affected. Both estimates are maximum figures, since families in which there are few affected may be excluded owing to non-recognition of familial tendency.

SUMMARY.

One of every 600 children born alive in Tasmania suffers from cleft lip and/or cleft palate, the highest recorded incidence for a community of European stock. Of these, 32·5% have a family history of the anomaly. On this basis alone, it would seem unwise that migrant families known to carry the trait should be freely admitted to the community.

Cleft lip and palate defects are almost equally prevalent throughout all districts of the State, and occur with the same frequency in rural and urban areas.

The hereditary basis of cleft malformation involving the lip and palate is examined. It is concluded, contrary to the currently accepted view of Fogh-Andersen, that cleft lip with or without cleft palate is not occasioned in all cases by a genetic system independent of that producing cleft palate alone. It is, however, true that at least two main genetic complexes are involved. One or more dominant autosomal genes of reduced manifestation probability are responsible in each case.

There is a significant excess of children with these anomalies born to mothers in the higher age groups; the effect of birth rank is probably related to this.

Empirical risk tables for cleft lip and palate defects in the Tasmanian population are presented as an aid in genetic counselling.

ACKNOWLEDGEMENTS.

This work was carried out with the financial support of the National Health and Medical Research Council (Australia). Many persons were helpful to our project. Special gratitude is expressed to the then Minister of Health, Dr. R. J. D. Turnbull; to the Director of Medical Services, Dr. J. Edis, and his assistants; to the medical superintendents of the Tasmanian hospitals and their record staffs; and to the many members of the practising medical profession of Tasmania who contributed information.

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A COOLING UNIT FOR SHEARING SHEDS.

By B. G. LUCAS, M.B., B.S.,
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THE question whether the Australian economy can be still said to be "riding on the sheep's back" is a debatable one. However, the fact remains that the wool industry is still of utmost importance, and that the shearing of fleece is one of its main components, there being approximately 50,000 employed in the pastoral industry in 20,000 shearing sheds.

Shearing for the most part in northern New South Wales and adjacent Queensland is carried out in the warmer months, to coincide with the low incidence of clover, noogoora and Bathurst burrs in the wool, and

FIGURE I.
The unit, mounted on a trailer attached to a conventional type light panel van, ready for towing.

to minimize the risk of cold in the shorn sheep and lambs—many losses being incurred in unseasonal cold snaps.

In the main, shearing sheds are constructed of galvanized iron, without much attention to adequate ventilation. Outside shade temperatures are greatly magnified within the shed, because lack of convection and conduction causes an oven-like effect made worse by the constant ingress of sheep hot from standing in the sun.

The work is hard, manual and competitive; the average number of sheep shorn per man is in the region of 115 per day, the shearer being paid on a piece-work basis. Each shearer thus strives to keep within close tally of the "ringer" (the one shearing the greatest number), so that his cheque is not (in shearing parlance) "unduly cut into".

In contradistinction, cooks, pressers, shed hands and rouseabouts are paid a weekly wage independent of the number of sheep shorn and not affected by shearing interruptions—for example, time lost through wet sheep, etc.

Food is rich and plentiful with a high carbohydrate content, an approximate average intake per man being in the region of 5000 Calories per day. These are

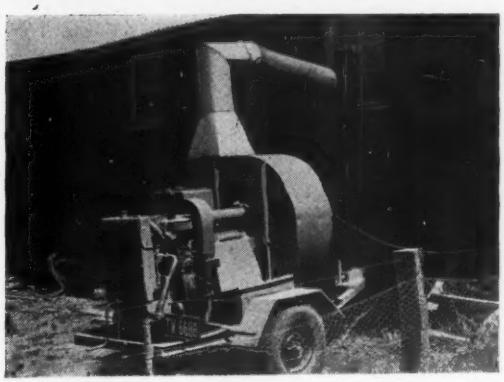

FIGURE II.
The unit, with water hose attached, playing into weatherboard shearing shed, the only alteration to the shed being the removal of two panes of glass.

ingested in three main meals, together with two tea breaks—"smokos"—when sandwiches and cakes are in abundance. Examples will be shown later.

Obesity is very uncommon amongst shearers in work, the arduous nature of which (standing with the back bent, firmly clasping and manipulating a five-pound

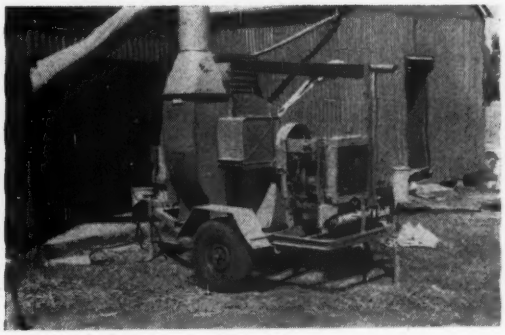

FIGURE III.
The unit blowing its cooled air into the mess hut.

handpiece and struggling with sheep sometimes weighing 200 lb.) adequately accounts for the expenditure of so many Calories in an eight-hour working day.

Physical exertion in a hot environment, when cardiac output and vasomotor control are inadequate to meet the demands of increased circulation to skin, cerebrum and working skeletal musculature, results in heat stress and exhaustion. This is made worse by minor and major degrees of dehydration and salt depletion. Whereas the frequent complaint of heat cramps—the painful contraction of various skeletal muscles (sometimes even causing respiratory embarrassment when intercostals and diaphragm are affected)—is adequately controlled by

increasing the salt intake, the distressing symptoms of faintness, nausea, lack of appetite, abdominal colic, vomiting, diarrhœa, headache, restlessness and inability to sleep provide shearers in hot climates with much actual discomfort and result in varying degrees of time lost. In one shed in extreme heat, temperatures were found to reach a maximum of, and to stay in the range of, 125° F. Shearing was impossible for any sustained

FIGURE IV.

The unit blowing air directly into the shed across the shearers and cooling the whole board. Sheep dog enjoying the cool. The only alteration to the shed was the removal of one sheet of galvanized iron.

period, the shearer having to rest and cool off after shearing two or three sheep.

The prevention of such symptoms and their subsequent economic loss prompted the following experiment. It was suggested that the shearers or, preferably, the whole shed be cooled by means of a portable fan. (Air conditioning in this country is not new. It is employed in many industries, and brings benefits to both manual and white collar workers alike; package units and individual room

FIGURE V.

The unit. Air directed to blow across shearers. Sheep dogs taking advantage of the cool air.

units are available for the home and the housewife, whilst its benefits to the newborn, the gravely ill and the aged need no mention here. However, the cost of installation, together with the infrequent use of sheds, has excluded such refinements from the shearing industry.) Technical details were provided by a mining engineer well versed in long-distance and low-level ventilation. The ideal was found to be in a 19-inch inlet fan, which provided, at 950 r.p.m., an air shift of 6000 cu. ft. per minute, the pressure being equivalent to three-inch water gauge. The necessary motive force was provided by a stationary 7·5 horsepower "Coventry Climax" petrol engine using approximately half a gallon of gasoline per hour. The movable parts—main fan, cooling fan to the motor and drive belts—were adequately guarded to prevent accidents and to comply with safety regulations. The whole unit was compactly mounted on to a two-wheel mobile trailer, the gross over-all weight being 15 cwt. 3 q. It could thus be towed easily by a conventional light vehicle and moved to suitable vantage points in shade around shearing shed, mess huts, etc. By spraying a fine jet of water vapour over the inlet, the component parts of the fan and the delivered air could be cooled, and then, according to the temperature and the requirements within the shed, could be either directed throughout the whole shed or individually ducted to play on the "board" in front of each shearing stand, thus

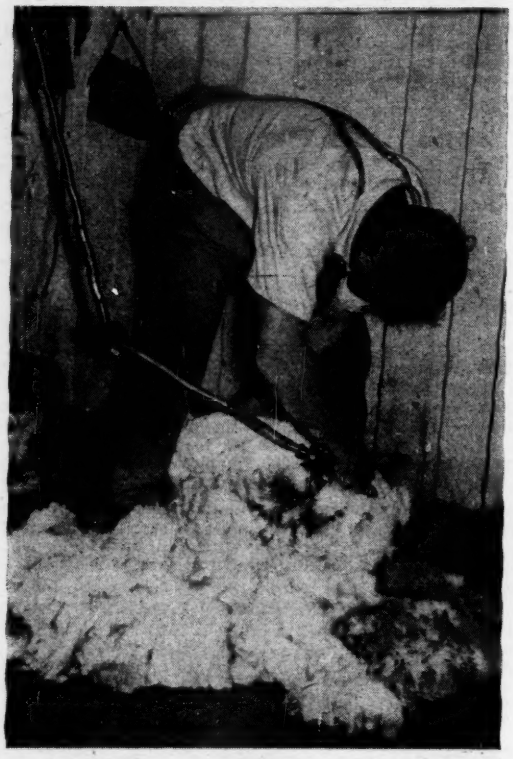

FIGURE VI.

A shearer in typical pose with the back bent. Sheep dog in background taking advantage of the cool.

cooling down each individual shearer. The unavoidable rise in humidity by such method is of no import in the hot arid west.

The following facts demonstrated without question the efficiency of the unit.

Shed I.

When the outside shade temperature was 108° F., the registration inside the shed was 125° F. An average of only three sheep could be shorn continuously, the prodromal symptoms of heat exhaustion forcing each man to rest. The following day, inside readings were again 125° F. After half an hour's running of the fan, the inside temperature had fallen to 86° F. No shearing time was lost, no shearers were inconvenienced by sweat or other untoward symptoms. An increased appetite is shown by the menu and food expenditure for that day, the provisions for 12 men being as follows:

Breakfast:

Rolled Oats	8 oz.
Chops	24 (6 lb.)
Rissoles	24 (4 lb.)

Eggs	12
Bacon	1 lb.
Toast	12 pieces
Bread	12 pieces
Butter	8 oz.
Marmalade	1 oz. per man per day (total 12 oz.)
Milk	6 oz. per man (total 72 oz.)
Sugar	1 oz. per man (total 12 oz.)

"Smokos"—morning and afternoon tea breaks:

Bread	one and a half large loaves
Butter	half a pound
Ham	one-eighth of a pound
Tomatoes	1 lb.
Cheese	quarter of a pound
Cakes ("patty")	3 dozen
Biscuits (oat)	3 dozen

This was a 50% increase over the previous day.

Luncheon:

Cold meat	8 lb.
Potatoes (baked)	5 lb.
Lettuce	1
Tomatoes	2 lb.
Beetroot	1 lb.
Onions	1 lb.
Cheese	quarter pound
Ice cream	4 quarts
Jelly	1 quart
Fruit salad	3 lb.

The luncheon intake remained virtually the same as on the previous day.

Dinner:

Soup (chicken and vegetable) ..... 3 quarts

Entree—

Braize	3 lb.
Curry and Mince and Rice	2 quarts
Baked meat	8 lb.
Boiled corned meat	4 lb.
Potatoes	5 lb.
Pumpkin	3 lb.
Cabbage	2 lb.

This showed a 40% increase over the previous day whereas the fruit intake at that meal remained the same—two pounds of pineapple and one dozen pieces of mixed fruits.

Shed 11.

The outside shade temperature was 108° F., the temperature inside the shed was 110° F., and after the fan had been set in operation the inside temperature fell to 68° F. No time was lost. Six men crutched 3200 sheep on that day. (This compares more than favourably with the same shed last year, when the outside shade temperature was 103° F. and only 1740 sheep were crutched by the same shearers.)

Conclusion.

The fan has provided a boon to all in the shed (including the hard-working sheep dogs, which often took some coaxing back to work in the hot sun), making working conditions more pleasant and healthy without time loss, and thus benefiting both employer and employee. It may also find a place in the drying of sheep; wet weather accounts for much time loss and lack of production, at least two days of fine weather being needed for sheep to dry.

It would seem that the fan has been an important and relatively inexpensive advance in both public health and industrial medicine, not to mention economic benefits, in the shearing industry. It is not hard to envisage the time when it will be standard equipment in our outback.

Acknowledgements.

My thanks are due to Mr. W. O. Thomas, of Thorley and Thomas, Inverell, for putting the idea into practice in the design and assembly of the plant, and to Mr. Bert Lowrey, shearing contractor, of Inverell, for financing the idea and using it in sheds under his control, and also for providing temperature readings and victualling details.

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THE AMMONIA CONTENT OF STORED BLOOD.

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EVER since Van Caulaert and his colleagues suggested that a relationship existed between blood ammonia levels and the course of certain hepatic diseases, there have been attempts to correlate the blood ammonia level with the mental state of the patient. Much work has been done in this field, beginning with an excellent monograph by Kirk (1936); but contemporary writers, such as Fazekas *et alii* (1956) and Summerskill *et alii* (1957), reiterate that there is no quantitative relationship between the degree of elevation of the blood ammonia level and the severity of any attending neurological disturbance.

Greenberg *et alii* (1957) have demonstrated that the ammonia content of stored whole blood rises while it remains stored, a point of obvious importance, in view of the frequent need to transfuse patients with cirrhosis of the liver and other diseases of the liver. It was decided to determine the ammonia concentration in blood used for transfusion in Sydney.

Material.

Through the courtesy of the New South Wales Red Cross Blood Transfusion Service, three samples of whole citrated blood were obtained on the day on which they were taken. The samples, each of approximately 75 ml., were received in a number of small "pilot" bottles, each containing sufficient blood for one day's estimation. These bottles were kept refrigerated during the investigation, in conditions similar to those in which blood is normally stored before it is given.

The conditions which apply to the health of donors giving blood to the Red Cross Blood Transfusion Service are designed to eliminate the possibility of hepatic disease, and therefore the possibility of a high ammonia level in collected blood at the time of donation is remote.

Method.

The method used for determining the blood ammonia content was basically the microdiffusion technique of Conway (1939, 1947) with minor alterations. In spite of certain difficulties with this method and the appearance of other apparently better methods (Seligson and Seligson, 1951), the method of Conway seems to be the most satisfactory available and the most generally used (Varay, 1957; Lieber and Lefèvre, 1958). Daily estimations in duplicate were performed on one divided sample from each of the three donors, with blanks and standard controls. These daily estimations were made for 18 days, which is slightly longer than the maximum period for which blood may be stored before it is given.

Results.

The range of normality is variable, but is generally accepted as being below 50 to 75 μg. per 100 ml. (Greenberg *et alii*). A group of 12 normal persons from this Unit was studied, and the values were 20 to 60 μg. per 100 ml., with a mean value of 45 μg. per 100 ml. In

[1] Supported in part by the National Health and Medical Research Council of Australia.

general, values of less than 100 μg. per 100 ml. are accepted here as being normal.

The results of the investigation are set out in Table I. It is of interest to note that the ammonia level of each of the three samples was well within normal limits on the first day, but that within two days it had risen to definitely abnormal levels. The over-all results, set out graphically in Figure I, showed a general upward trend in the blood ammonia level over the period of the investigation, reaching a peak of approximately 300 μg. per 100 ml. by the eighteenth day.

TABLE I.[1]

Day.	Sample I.	Sample II.	Sample III.
1	65	65	55
2	85	90	105
3	150	150	150
4	150	160	155
5	145	150	160
6	155	160	185
7	170	165	180
8	190	175	185
9	225	210	180
10	240	205	210
11	235	220	225
12	255	235	240
13	285	245	255
14	295	240	250
15	300	255	265
16	310	270	280
17	325	285	300
18	335	290	300

[1] The results are expressed in microgrammes per 100 ml.

Discussion.

As has been previously mentioned, there is no good correlation between the blood ammonia level and the presence or absence of hepatic coma such as there is between the blood glucose levels and hyperglycæmic coma; it is well recognized that a patient in hepatic coma may have a normal blood ammonia level. Similarly, a patient who shows no sign of impending hepatic coma may have a considerably raised blood ammonia level (Chaikin and Konigsberg, 1959; Varay, 1957). There is also experimental work to support these findings (Handford, 1959). However, Lieber and Lefèvre (1958) have recently suggested that while the relationship between the venous blood ammonia levels and the mental state of a cirrhotic patient is not good, there is a definite relationship between the arterial blood ammonia level and the mental state.

Cincotti (1955) stated that, in his experience, the ammonia levels of stored blood ranged from 9 to 900 μg. per 100 ml. within three weeks of collection. Greenberg *et alii* (1957) sampled at random a number of bottles of blood up to 68 days after collection, and found ammonia levels which ranged from 20 to 600 μg. per 100 ml., although at 21 days (the time of expiry set by the San Francisco Blood Bank) most levels were below 250 μg. per 100 ml. Although these results were lower than those of Cincotti, it was suggested that the discrepancy might be explained by differing methods of collection and storage, and by variations in the technique of blood ammonia determination. Fabiani *et alii* (1958) also mention that the ammonia content of stored blood increases after long preservation.

The results of this present investigation have shown a fairly constant rise in the ammonia levels of stored blood, from initial normality to levels at 18 days which might be expected in hepatic precoma or even frank hepatic coma.

Just what is the fate of the free ammonia contained in stored blood once it reaches the patient's circulation is not known. Presumably it passes through the normal processes of metabolism after permeating into the tissues, provided that the normal processes of metabolism are not inactivated.

The ammonia content of a litre of blood stored for two weeks (assuming the blood to have an ammonia level of 250 μg. per 100 ml.) would be approximately equivalent to 30 mg. of ingested ammonium chloride. This is not a large amount, and as Greenberg points out, it may well be of debatable clinical significance. However, there are two possible situations in which the implication of these findings is applicable. It is conceivable that a patient with an already elevated blood ammonia level might suffer adverse effects from the ammonia content of a reasonably small quantity of long-stored blood. On the other hand, whole bottled blood with a high ammonia content is far more likely to cause a significant rise in the blood ammonia level of those patients with cirrhosis who are bleeding profusely from varices into the alimentary tract, and who need large volumes of blood to keep them alive.

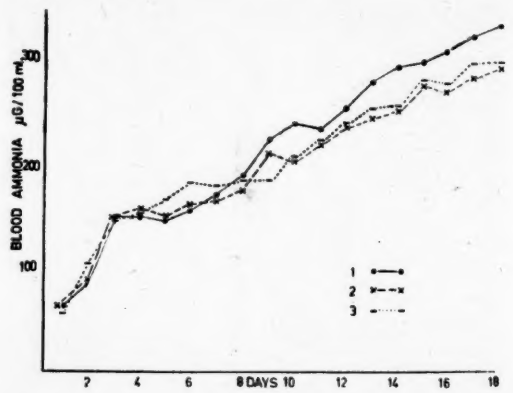

FIGURE I.

Thus the present finding of a progressively increasing ammonia content in stored blood implies that when a transfusion is given to a known cirrhotic patient, or to a patient who is suspected to be bleeding from varices or other gastro-intestinal lesion and is approaching hepatic coma, it is necessary to use blood which is as fresh as possible. This principle applies even more strongly when an heroic attempt is made to salvage adult patients from hepatic failure by exchange transfusion.

Summary.

1. Daily estimations of blood ammonia content were made on three samples of stored blood for eighteen days. A steady rise from normal levels (50 to 60 μg. per 100 ml.) to abnormal levels (290 to 335 μg. per 100 ml.) was observed.

2. It is suggested that it is advantageous to use blood which has only recently been collected when giving a transfusion to a patient who is bleeding into the bowel, and is in danger of going into hepatic coma.

Acknowledgements.

I wish to acknowledge with gratitude the cooperation of Dr. R. J. Walsh, Director of the New South Wales Red Cross Blood Transfusion Service, for providing the blood samples used. I also wish to thank Professor C. R. B. Blackburn for his encouragement and advice.

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MINIMAL DRUG DOSAGE IN THE PRACTICE OF ANÆSTHESIA.

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IT is a curious thing that in relation to most subjects there is often some aspect, frequently quite an important one, to which very little attention is paid. It is my belief that the matter of dosages of drugs and agents used in anæsthetic practice falls into this category.

As all the drugs and anæsthetic agents used in anæsthetic practice are toxic to a greater or less extent, it follows that, provided optimal conditions for surgery are attained, then the best results, both during the operation and after it, will be gained by the use of the smallest doses possible. The beginner in the practice of anæsthesia frequently uses unnecessarily large doses, but with experience employs smaller and smaller doses with progressively better results.

At first sight, one might think that the simple avoidance of excessively deep premedication and anæsthesia would accomplish all that was necessary. However, I think the matter is somewhat more complicated than this, and I should like to discuss in greater detail some of the opportunities which exist for reducing dosages of drugs and agents during the different stages of anæsthetic administrations.

Pre-Anæsthetic Medication.

Drugs administered pre-operatively should be related both in nature and in dosage to the patient, his illness, the operation and the proposed anæsthetic technique. Variation is therefore essential. Often in the interests of uniformity and simplicity there is a tendency to administer pre-anæsthetic medication on a "routine" basis. Under such schemes, frail patients may easily receive relative overdoses. At other times, premedication may be correct in regard to dosage, but inappropriate from a pharmacological point of view. A small dose of a suitable drug is more effective than a large dose of a less suitable one. For example, if the operation is for meniscectomy (a procedure ordinarily followed by severe pain), an average dose of pethidine would be better than even a large dose of barbiturate or chlorpromazine. In contrast, many of the orthopædic manipulations (with subsequent plaster application) performed on children are almost painless after operation. There is therefore no need for analgesic drugs; but, since these children are apprehensive and subject to many trips to the operating theatre, sedatives are desirable. Thiopentone administered rectally is particularly suitable.

In the past it has been common to premedicate patients about to undergo operations under local or regional analgesia so heavily that the result has often been the attainment of something akin to general anæsthesia. It is generally considered now that it is better to "cover" the local analgesic method with general anæsthesia produced by nitrous oxide, reinforced if necessary with traces of more potent agents.

In recent years there has been a tendency to increase the dosage of atropine. This has the disadvantage of further upsetting heat regulation, and in hot climates can have serious consequencies. It is my belief that the dose of atropine formerly used (0·6 mg. for an adult) is still the correct one.

Induction of Anæsthesia.

Most anæsthetists use thiopentone frequently for the induction of anæsthesia, and are thoroughly familiar with the dosage necessary for a healthy adult. Proportionately smaller doses are necessary for children; but for the old, the frail, the desperately ill or the injured, the doses that may be safely used are very small indeed. In addition, since in these groups of patients the circulation rate is slow, the thiopentone must be injected at a reduced rate, with longer intervals between injections for it to take effect.

Intubation is a procedure in which larger doses of general anæsthetic agents and relaxants are often employed than would be necessary if the instruments and tubes were used in the way intended by the designers. The Macintosh and the Magill laryngoscopes are both designed to be used in the right side of the mouth, and likewise the Magill tube is intended to be introduced from the same side. Any shifting of the approach to the left increases the difficulty of the manœuvre. If the Magill tube is held with the concavity directed exactly forward, then the bevelled end of the tube will slip between the vocal cords like a wedge. At times patients will be encountered in whom, for anatomical reasons, intubation is almost impossible. Under such circumstances one may be tempted to give more anæsthetic agent or relaxant, although the difficulties are not due to deficient relaxation. In these patients the use of an introducer can often help tremendously. The Oxford introducer is one satisfactory type. There was a time when I thought that endotracheal introducers (along with motor-car heaters and automatic motor-car transmissions) should be scorned by all red-blooded anæsthetists; but now I have changed my mind (in regard to all three), and believe that an introducer is an essential part of one's equipment. At times nasal intubation may be performed when oral intubation is very difficult.

At times the application of local analgesic agents to the larynx will enable an intbuation to be performed with small doses of anæsthetic and relaxant agents.

Maintenance of Anæsthesia.

Nitrous oxide is by far the least toxic of all inhalational anæsthetic agents, and its administration in combination with other inhalational agents substantially reduces the amount of the more potent (and more toxic) agent necessary.

One of the most commonly used anæsthetic methods at the present time is that of an induction with thiopentone and relaxing agent, followed by intubation and the administration of nitrous oxide and oxygen by controlled respiration, with subsequent further injections of relaxing agent, pethidine or thiopentone. I believe the following suggestions will help towards the aim of using minimal doses.

1. Use just sufficient drugs to effect an atraumatic intubation. Do not try to assess the total dose of relaxant

for the whole operation and inject it in one lot. If one tries to use small doses, it will be found that often the whole operation of hysterectomy or cholecystectomy can be performed on an intubating dose of 80 mg. of "Gallamine".

2. Administer further doses of relaxant only when required. Usually 20 mg. of "Gallamine" or 5 mg. of "Tubarine" are sufficient in a healthy adult to give useful periods of relaxation, without the danger of gross relaxation at the end of the operation.

3. When operating conditions become unsatisfactory, try to decide whether a relaxant, an analgesic or thiopentone is required. If the correct drug is used, the effect is usually more marked and of longer duration than otherwise.

4. If at the end of the operation relaxation is insufficient for peritoneal closure, do not give a full fractional dose of relaxant. Give either 10 mg. of "Gallamine" or 3 mg. of "Tubarine". Alternatively, 0·1 gramme of thiopentone or a trace of "Halothane" added to the nitrous oxide will often be satisfactory.

5. Make sure that carbon dioxide absorption is satisfactory. I believe that, in the past, difficulties in maintaining control of respiration have often been related to inadequate carbon dioxide absorption, with a consequent pronounced tendency to the reassertion of spontaneous respiration. With the use of efficient absorbers, particularly the recently introduced two-canister type, one finds that more long-lasting effects can be obtained from the drugs used.

Post-Operative Period.

Anticholinesterases are commonly given at the conclusion of an anæsthetic administration, to reverse residual relaxation following the use of "blocking agents". If one has used minimal doses of relaxing agents, it is also possible to use minimal amounts of anticholinesterases. Often one can attain an entirely satisfactory return of muscle power after the injection of 0·5 to 1 mg. of neostigmine following 0·6 mg. of atropine. One cannot rely on large doses of anticholinesterases to reverse really marked relaxation; when optimal dosages are exceeded, further amounts may even produce harm.

Narcotic and barbiturate antagonists are sometimes necessary; but again, if caution has been used in the administration of analgesic drugs and barbiturates, the amounts of the antagonists necessary will be small.

Local Analgesic Drugs.

Those who do not use local analgesic techniques often are apt to administer unnecessarily large doses on the occasions when they do, in the hope that in this way success will be achieved. The action of the local analgesic agents (lignocaine, procaine, amethocaine, etc.) is completely predictable. If the correct strength of the agent is injected in the correct location, then the desired analgesia will result with a certainty equalling that of general anæsthesia. One should know the maximum doses of the various agents and not exceed them. The addition of adrenaline, and at times of hyaluronidase, will often assist in attaining the desired effect, with a dosage still within safe limits.

Adrenaline is frequently administered, by injection and by application, in excessive concentrations and in excessive total dosages. In comparison with correct usage, these excessive amounts do not produce a sufficient improvement in local operating conditions to offset the undesirable systemic effects that accompany their use. I think that most anæsthetists would regard a 1:250,000 concentration of adrenaline as a suitable one for injection, the maximum total dosage being 500 μg. of adrenaline.

Summary.

The desirability of using minimal doses of all anæsthetic agents and of all drugs used in anæsthetic practice has been stressed.

An attempt has been made to show the means whereby dosage of drugs can be reduced to a minimum in relation to pre-anæsthetic medication, induction of anæsthesia, maintenance of anæsthesia, the post-operative period and local analgesic techniques.

THE HISTOPLASMIN SKIN TEST: A BRIEF REPORT.

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THAT clinical cases of histoplasmosis do occur in Australia has become apparent from published reports of four cases (Johnson and Derrick, 1948; Inglis and Powell, 1953; Dowe *et alii*, 1953; Ridley and Nowell, 1959). A histoplasmin skin testing survey undertaken in 1953 was reported by Ridley and Nowell (1959), when probably positive skin reactions were obtained from six patients.

Histoplasmin skin tests were performed on three of the four patients whose cases were described in these reports. From the full descriptions given, the diagnosis does not seem to be in doubt in any case; yet the response to the histoplasmin skin test was recorded as negative in the case described by Inglis and Powell. The result was not recorded in the case described by Johnson and Derrick, but was positive in the other two instances recorded. A negative response to the histoplasmin skin test therefore does not exclude a diagnosis of histoplasmosis. On the other hand, it is accepted that a positive response does not necessarily mean that active histoplasmosis is present.

Because of these reports, it was decided to perform intracutaneous histoplasmin skin tests on symptomless persons whose routine chest X-ray films taken at the Brisbane Chest Clinic showed scattered round calcified foci. No attempt has been made to carry out a general skin-testing survey of patients presenting for chest X-ray examination, and the patients tested were a highly selected group. Eight patients whose chest X-ray films show calcified deposits have been found to give a positive reaction to the intracutaneous histoplasmin skin test. An area of induration 10 mm. or more in diameter at the site of injection of 0·1 ml. of a 1:100 dilution of histoplasmin skin-testing antigen, when read at 72 hours, has been regarded as a positive result as far as this investigation is concerned.

Details of the eight patients with positive results are set out in Table I. They were all male.

Comment.

These results demonstrate that in some people who have never been outside Australia, and also in other people who have no symptoms and who, in fact, can remember no serious previous illness, a positive skin reaction to histoplasmin can be found. It is pointed out, however, that during the course of this survey, some patients whose chest X-ray films revealed abnormalities which could not be distinguished from those in this series have been found to give a negative response to histoplasmin skin tests.

It is possible that more clinical cases of histoplasmosis occur in Australia than are recognized at present. The wider use of the histoplasmin skin test in the investigation of patients with acute or chronic pulmonary disease (and not only of symptomless individuals whose routine chest X-ray films show evidence of scattered round calcified foci, as in this present survey) would, it is thought, be wise.

It is considered of interest that two of these eight subjects are coal-miners and work underground, and that a third had been a miner for four years in the past.

It is noted also that the two subjects with the strongest reactions to histoplasmin (15 mm. of induration) were both men who had not been out of Australia.

TABLE I.

Subject Number.	Date of Birth.	Occupation.	Domicile.	Chest X-ray Appearances.	Response to Tuberculin Skin Test and Type.	Diameter of Positive Histoplasmin Reaction.
I	1913	Meter-reader.	Always in Australia, mainly Queensland.	A few calcified lesions in both lungs, each slightly irregular in outline, but mainly circular, from 2 to 10 mm. in diameter. Most of the opacities are about 5 mm. in diameter.	Positive Grade III (Heaf). All the Heaf tests were performed with undiluted old tuberculin.	15 mm.
II	1910	Farmer.	South Queensland only.	Moderate number of round calcified nodules scattered throughout both lungs. The majority of the opacities are approximately 3 to 4 mm. in diameter.	Negative.	15 mm.
III	1898	Engineer.	Queensland and New Zealand.	Very similar in all respects to Subject I.	Positive (Heaf).	10 mm.
IV	1893	Miner — previously lead and silver, now coal.	Virginia, U.S.A.; Queensland since 1925.	Similar to Subject II, except that the lesions are not quite as numerous and tend to be very slightly larger.	Positive Grade III (Heaf).	10 mm.
V	1920	Coal-miner for 16 years.	Australia only, except for 4 months in New Guinea.	Numerous scattered small round opacities, less dense than the lesions in most other X-ray films in the series. The opacities are all small, only one or two being over 2 mm. in diameter.	Positive Grade IV (Heaf).	10 mm.
VI	1903	Seaman and clerk. Hard rock mining in Queensland, 1930 to 1933.	England, Germany, Canada, Mediterranean area, South America. Australia since 1927.	Very similar in all respects to Subject V.	Positive intracutaneous old tuberculin (1/1000).	10 mm.
VII	1905	R.A.F. pensioner.	England, Borneo, New Guinea and Australia.	Numerous scattered, well-calcified nodules in both lung fields, more marked in middle and lower zones than in upper zones. Most of the individual lesions are about pin-head size or slightly larger (2 or 3 mm. in diameter).	Positive Grade II (Heaf).	12 mm.
VIII	1921	Freezer in meat-works.	Italy and Sicily. Australia since 1957.	A group of five irregular calcified nodules in left lower zone each 3 to 5 mm. in diameter. Moderate number of smaller round nodules scattered throughout right upper and middle zones averaging about 2 mm. in diameter.	Positive Grade IV (Heaf).	12 mm.

Acknowledgement.

The histoplasmin skin-testing antigen used in this survey was kindly supplied by Dr. M. L. Furcolow, Kansas City Field Station, 3900 Eaton Street, Kansas City 3, Kansas, U.S.A. His help in this regard is greatly appreciated.

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THE ELECTRIC FRYPAN AS A DRY-HEAT STERILIZER.

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IT has been suggested (Davis, 1959) that the electric frypan would make an efficient hot-air sterilizer for surgery use.

As the electric frypan is very much cheaper than an orthodox dry-heat sterilizer, we decided to test it. For this purpose a frypan with a hole drilled in the glass lid to take thermocouple wires was supplied by the manufacturer. In the first test, a half-ounce jar full of white petroleum jelly was placed on a fibrocement sheet drilled with holes to enable heat to rise from the base of the pan. The thermostat was set at full (216° C. = 420° F.). After 55 minutes, the temperature in the centre of the petroleum jelly was 116° C. (241° F.), and at the end of two hours it had risen to 134° C. (273° F.). The temperature on top of the base at that time was 153° C. (307° F.). When the fibrocement base was replaced by a gauze mat which raised the jar about half an inch above the bottom, the temperature in the petroleum jelly did not exceed 140° C. after 145 minutes at full heat. The temperature on top of the gauze reached 157° C. (315° F.) in that time. (For effective sterilization, this quantity of petroleum jelly would need to be exposed to a temperature of 160° C. for at least an hour, though two hours is desirable.)

One ounce of talcum powder was spread evenly in a petri dish (3·5 inches in diameter) so that the layer was about a quarter of an inch thick. The thermostat was set at 191° C. (375° F.). It took 90 minutes for the temperature in the centre of the powder to reach 149° C., and when the layer of talc was one inch deep, the temperature did not rise above 146° C. in the same time. The temperature on top of the gauze was 164° C. (327° F.).

An all-glass syringe of a capacity of 5 ml. was placed on the gauze base and the thermostat set at 191° C. (375° F.). After one hour, the temperature inside the syringe was 143° C., and the temperature on the outside of the syringe was 145° C. The gauze temperature was 160° C. (320° F.). (For dry-heat sterilization of syringes, a temperature of 160° C. for one hour is required.)

It is apparent that the electric frypan is not a reliable dry-heat sterilizer. Orthodox dry-heat sterilizers have insulated walls and all-round heating elements, and some have fans to ensure even heat distribution. The electric frypan has a heating element only in the floor, and has no special insulation to prevent heat loss. There is, therefore, a steep fall in temperature from the bottom to the lid of the pan. This is confirmed by the large differences in temperature between the objects being sterilized and the temperatures just above the base. Thus, adequate sterilization of the whole of an article in the frypan can be achieved only by greatly overheating its bottom portion and carefully measuring the temperature of its coolest part. In other words, the electric frypan has been designed to fry and not to sterilize.

We believe that the results of these tests should be of interest to readers.

Reference.

DAVIS, R. C. (1959), "A Frypan as a Sterilizer", MED. J. AUST., 2: 297.

Reports of Cases.

SUBCUTANEOUS FAT NECROSIS OF THE NEW-BORN.

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SUBCUTANEOUS FAT NECROSIS of the new-born is an uncommon condition, generally regarded as benign in nature. In the case to be presented this condition was associated with sclerema neonatorum and complicated by two episodes, one of which seriously endangered the life of the patient.

Clinical Record.

The mother of the patient, Mrs. A., was a primigravida, aged 25 years. Her pregnancy was complicated in the last trimester by toxæmia and pyelitis, which necessitated her admission to the Newcastle Western Suburbs Maternity Hospital 24 days prior to her estimated date of confinement. The toxæmia did not respond to routine measures, and a medical induction of labour was instituted two weeks after her admission. Three days later, after a prolonged first stage and precipitate second stage of labour, she was delivered of a male infant weighing 8 lb. Meconium-stained liquor was observed before delivery.

The infant was in poor condition in the immediate neonatal period. He was slow to breathe and to cry, and was given oxygen in the labour ward and later placed in a humidicrib. Respiration remained rapid, grunting and shallow in nature and his colour dusky, without oxygen, for some two hours, after which there was a gradual improvement. At the age of four hours the patient was taken out of the humidicrib.

On the third day of life an area of subcutaneous fat necrosis approximately 1·5 in. square was noticed on the infant's back, with smaller areas on the outer surface of the arms, the buttocks and thighs. The skin over these areas was raised and reddened, and the underlying subcutaneous tissue was indurated and felt nodular. Palpation of these areas appeared to cause pain. At this stage the baby was lethargic, with weak, poorly-sustained sucking; his respirations were shallow and rapid and he vomited frequently. Because these symptoms were associated with mild pyrexia and occasional cough, chloramphenicol (125 mg.) was given every six hours.

Commencing late on the third day, there developed the generalized, woody, non-pitting stiffening of the tissues characteristic of sclerema neonatorum. By the following day this process had intensified, and the condition of the patient deteriorated still further. Marked lethargy, failure to suck, weak respiratory efforts, minimal response to external stimuli and subnormal temperature were observed. Methyl-prednisolone ("Medrol"), 2 mg. three times a day, was given on the fourth day, followed by 2 mg. twice a day on succeeding days.

In the next four days the patient's condition remained grave. Tube feeding was necessary, vomiting was frequent and there was a gradual loss of weight. By the seventh day of life there was a noticeable diminution in the intensity of the sclerema neonatorum, allowing a gradual reduction in the dosage of "Medrol"; but there was no concomitant improvement in the health of the infant. The clearly demarcated areas of subcutaneous fat necrosis had increased in size, especially the area on the back, which now measured some 3 in. square.

On the ninth day of life, there occurred a dramatic episode in the form of an exsanguinating hæmorrhage into the area of subcutaneous fat necrosis on the back (Figures I and II). This lesion was converted into a tense, bulging, purple bulla of blood, and the patient was rendered moribund. He was transferred to the children's ward of the Mater Hospital, Newcastle, where a transfusion of 300 ml. of whole blood was started, and approximately one hour later he was taken to the operating theatre. Here 250 ml. of fluid resembling blood was aspirated from the bulla, and it was observed that the

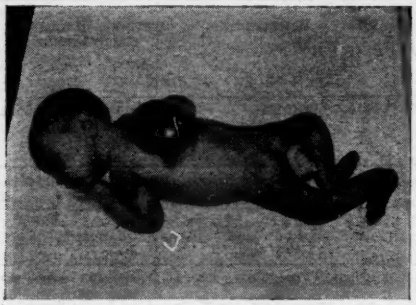

FIGURE I.

Hæmorrhage into an area of subcutaneous fat necrosis. The dark patches visible in the left deltoid region are areas of subcutaneous fat necrosis.

hæmorrhage had resulted from generalized oozing in the necrotic subcutaneous tissue. The redundant areas of skin were trimmed, a glove drain was inserted and pressure packs were applied to the affected area (Dr. D. G. Walker).

The progress of the patient continued to be slow, owing to poor sucking effort and persistent vomiting. This necessitated frequent recourse to tube feeding. Sloughing of a central area of skin in the affected area developed,

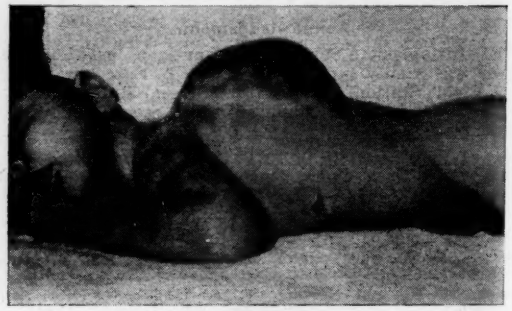

FIGURE II.

Hæmorrhage into an area of subcutaneous fat necrosis.

and on the twenty-third day of life a skin graft from a donor area on the thigh was applied. At the same time a biopsy was taken from the margin of the lesion. This was reported on as follows by Dr. K. H. White:

> The specimen consists of a small biopsy of skin and subcutaneous tissue. Microscopically, the epidermis is normal. There is an increase in fibrous tissue and collagen in the dermis, replacing some of the fat, and deeper in the dermis are some groups of foreign body giant cells around altered fat cells. Some of the fat in the cells is crystalline in form. A few scattered lymphocytes and plasma cells are present in this area.

The margins of the areas of subcutaneous fat necrosis all became progressively harder in texture giving the impression of calcification. A serum calcium estimation at the age of four weeks gave the figure of 11·6 grammes per 100 ml.

Eventually there was an improvement in the infant's ability to feed, vomiting became less frequent, weight gain became progressive, and at the age of five weeks, weighing 8·5 lb., he was discharged from hospital. The grafted area had healed (Figure III).

Two weeks later he was readmitted because of the development of a tender, red, fluctuating swelling overlying the areas of fat necrosis on the lateral surface of the left arm and extending into the neighbouring tissue

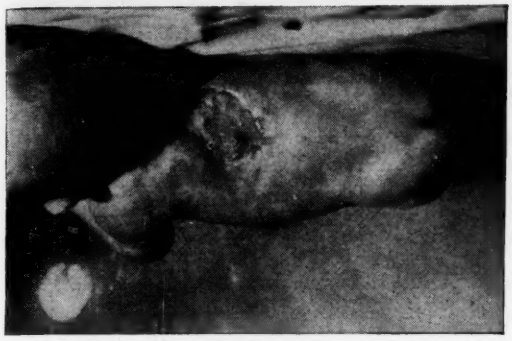

FIGURE III.
Healing lesion of subcutaneous fat necrosis with central grafted area.

(Figure IV). This was incised with the release of a large amount of pus, culture of which resulted in a profuse growth of penicillin-resistant, coagulase-positive *Staphylococcus aureus*. Rapid resolution of the infection followed the incision, but the baby's discharge from hospital was delayed till two weeks after his admission because of microcytic anæmia (hæmoglobin value 8·7 grammes per 100 ml.), which responded subsequently to iron therapy.

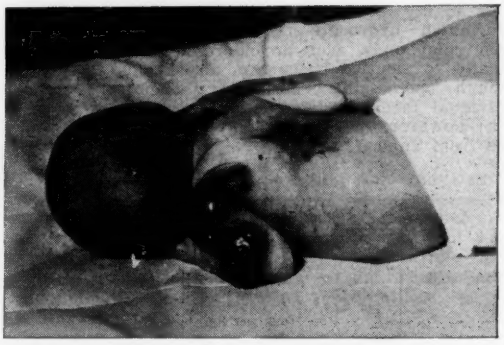

FIGURE IV.
Subcutaneous staphylococcal abscesses involving areas of subcutaneous fat necrosis in the left deltoid region.

The patient next was examined in the out-patient department at the age of 17 weeks, when he weighed only 10 lb. 12 oz. His poor nutritional state, together with marked gaseous distension of the abomen, resembled that seen in the malabsorption syndrome. However, there was no history of bowel dysfunction. The lesion on the back and the grafted area had made good progress, and the other areas of subcutaneous fat necrosis were no longer palpable.

At 25 weeks there was an obvious improvement in physique, and he weighed 17 lb. At the age of nine months, weighing 22 lb., he presented a picture of abundant health, and had passed the milestones of motor development appropriate for that age.

Discussion.

Sclerema neonatorum and subcutaneous fat necrosis of the new-born are two distinct and probably unrelated processes. McDonald (1955) and Browne and Burman (1958), have discussed their differentiating points and the suggested ætiologies.

The following description of sclerema neonatorum by Parrot is found in Henoch's book published in 1889, and quoted by Bower (1960):

> An induration and rigidity which the skin of the infant offers to pressure . . . [the skin] loses its softness; and finally can no longer be raised from the subjacent parts, to which it appears firmly attached . . . [it] soon acquires the consistency of thick leather. All soft parts then appear as rigid as wood or stone, there is no pitting on pressure.

The condition occurs in new-born infants, especially in premature infants and in those debilitated from any cause. Neonatal cold injury is another recognized predisposing factor (Mann and Elliott, 1957; Bower *et alii*, 1960). Sclerema neonatorum tends to be associated with a low body temperature, and the generalized rigidity causes resistance to passive movement of the limbs. The prognosis in this condition is generally grave, but may be improved by the administration of corticosteroids (Wright, 1954; Eisenhoff, 1954; McDonald, 1955; Wickes, 1956; Browne and Bowman, 1958). Because infection may be a major or associated ætiological factor, an antibiotic cover is indicated at least during the period of corticosteroid therapy.

Subcutaneous fat necrosis of the new-born is most likely to occur in infants with a history of asphyxia in the immediate neonatal period (Holzel, 1951). The affected areas, which may be single or multiple, are clearly demarcated from the surrounding normal tissue, and as a rule the overlying skin is raised and discoloured. The subcutaneous tissue gradually changes from a nodular firmness to a doughy consistency, and a return to normal can be anticipated within a few months.

The situation of the lesions appears related to areas of pressure from maternal, fœtal or instrumental parts. Fauser (1954) reported the occurrence of subcutaneous fat necrosis in monozygotic twins whose mother had a myomatous uterus. In one of the cases of Browne and Burman (1958), a large lesion on the back was shown by an ante-partum X-ray film to have been in contact with a calcified fibroid tumour during the pregnancy. Feldman (1957) reported a case in which pressure from a constriction ring was associated with a patch of subcutaneous fat necrosis on the shoulder. Lesions in this situation also may be due to the hands of the fœtus pressing into his own arms (Browne and Burman, 1958). Holzel (1951) and Feldman (1957) also reported areas developing at the site of pressure from obstetrical manipulations.

Other suggested ætiological factors associated with pressure are ischæmia (De Vel and Bolin 1929) and the low olein content of the subcutaneous fat of the new-born (Wright, 1954).

In Mrs. A no uterine fibroid tumour was identified, and the reason for the distribution of the lesions remains one of speculation.

The development of calcification in the necrotic tissue is not infrequent, and this has been associated with idiopathic hypercalcæmia (Clay, 1956). In the present infant there was a palpable sensation of subcutaneous calcification, although X-ray films of the areas at the age of 18 days did not confirm this. The failure to thrive, poor sucking effort and vomiting suggested the possibility of coexisting hypercalcæmia; but the serum calcium content was within normal limits.

Apart from calcification, the reported complications of subcutaneous fat necrosis of the new-born are atrophy of the involved subcutaneous tissue (Holzel, 1951) and radial nerve palsy associated with lesions on the corresponding arm (Feldman, 1957; Browne and Burman, 1958). In the series of Feldman, eight cases of radial nerve palsy in new-born infants were reported, and six of these were associated with areas of subcutaneous fat necrosis. In all six cases recovery of function was complete.

The occurrence of an exsanguinating hæmorrhage into an area of subcutaneous fat necrosis of the new-born apparently has not been reported previously. The ætiology of the hæmorrhagic episode in the present case was not

determined. The small amount of blood obtainable from the patient after the hæmorrhage was sufficient only for typing and cross-matching of his blood prior to transfusion.

It is presumed that this episode was a manifestation of hæmorrhagic disease of the new-born occurring in an infant who had received no vitamin K. The onset at the age of nine days is late for this condition, which usually occurs between one and four days after birth, coinciding with the period of lowest prothrombin levels (Gairdner, 1954). However, other factors may account for this late onset. Intrauterine asphyxia, such as this infant probably suffered, is associated with prothrombin levels lower than in normal infants (Dam *et alii*, 1952). Furthermore, any process injuring the fragile vascular system of the infant may precipitate a serious hæmorrhage in this susceptible immediate neonatal period (Quick, 1957), and capillary dysfunction also may be a factor predisposing towards hæmorrhage (Moloney, 1943).

It is suggested, therefore, that this hæmorrhage resulted from the combination of neonatal hypoprothrombinæmia, accentuated by intrauterine asphyxia, and capillary dysfunction and/or injury associated with subcutaneous fat necrosis.

The amount of blood lost from the circulation was large. Theoretically this infant, weighing approximately 3·5 kg., had a blood volume in the vicinity of 280 ml. (that is, 80 ml. of blood per kilogram of body weight—Smith, 1956). Yet 250 ml. of sanguinous fluid was aspirated from the bulla about an hour after the start of the transfusion, in which time there was little appreciable increase in the size of the lesion. The exact duration of the bleeding is unknown, but in retrospect it could have commenced up to 18 hours prior to the transfusion. Since a reduction of blood volume by 30% to 40% in an infant can end fatally unless restorative procedures are instituted immediately (Guest, 1954), it is surprising that this patient could have survived such an apparently greater blood loss.

Central liquefaction in areas of subcutaneous fat necrosis of the new-born may lead to an erroneous diagnosis of subcutaneous abscess, and one is warned against incising these lesions (Wright, 1954). However, in the present case a subcutaneous abscess did form in an affected area.

Clinically, the differentiating points from an "abscess" of liquefaction were the bulging nature of the fluctuant mass and the extension of the redness and swelling beyond the margins of the area of fat necrosis. Thus, infection in areas of subcutaneous fat necrosis of the new-born can be added to the list of manifestations of staphylococcal infection acquired in maternity units.

Summary.

A case of diffuse subcutaneous fat necrosis of the newborn is reported. The association with sclerema neonatorum, and complication by an exsanguinating hæmorrhage into one of the lesions and development of a staphylococcal subcutaneous abscess in another, are the unusual features discussed.

Acknowledgements.

My thanks are due to Dr. H. N. Rose, who referred this patient, and to Dr. D. G. Walker, of the Mater Hospital, Newcastle, who was responsible for the surgical management of the patient and for the photographs reproduced in this paper.

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ALDRIN POISONING: A CASE REPORT.

By Alan Bell, D.I.H.,

Director, Division of Occupational Health, N.S.W. Department of Public Health, Sydney.

Aldrin, the empirical formula of which is $C_{12}H_8Cl_6$, is a highly active and widely used member of the chlorinated hydrocarbon group of insecticides; many other compounds, such as chlordane, DDT, dieldrin and lindane, to mention but a few, also belong to this group. Though possessing dissimilar chemical structures, individual members have many toxic properties in common; however, they are not all equally toxic, as may be seen from Table I.

Table I.

Compound.	Acute Oral Approximate LD_{50} for Rats (mg. per kg.).[1]	Dermal (Single Exposure, 24 Hours) Approximate LD_{50} for Rabbits (mg. per kg.).[1]	Dangerous Acute Oral Dose to Man.[2]
Aldrin ..	67	< 150 (4%)	As for dieldrin.
Chlordane (technical)	457	< 780 (20%)	—
DDT ..	250	<2820 (30% (technical)	10 mg. per kg. produces illness in some subjects; doses up to 285 mg. per kg. have been taken without fatal result.
Dieldrin ..	87	150 (4%)	More than 10 mg. per kg. frequently causes acute illness.
Endrin ..	5 to 45	—	As for dieldrin.
Lindane ..	125	< 188 (2%)	Estimated at about 7 to 15 grammes.
Methoxychlor	6000	<2820 (30% technical)	—
Toxaphene ..	69	< 780 (20%)	Estimated to be 2 to 7 grammes.

It should be noted that the effects of dieldrin and aldrin on animals are similar, both quantitatively and qualitatively; this also appears to be true for man.

The active ingredient of any pest destroyer sold in New South Wales may be determined by reference to a publication issued by the New South Wales Department of Agriculture;[3] this free booklet lists by name some 1388 proprietary lines.

Formulations of aldrin, and the closely related insecticide dieldrin, may be used as wettable powders, as emulsifiable concentrates, as fogging solutions, as domestic sprays or as dusts. Both are readily absorped through the unbroken skin, respiratory passages and gastro-intestinal tract. Dry dieldrin and the solution are absorbed equally easily through the intact skin. However, a given amount of dieldrin is absorbed more readily by a large skin area than by a small one. This insecticide is less than twice as poisonous by mouth as by skin application.[4]

Signs and Symptoms of Poisoning.

It is unfortunate that there are no specific tests enabling one to diagnose with certainty either aldrin or dieldrin poisoning. A study of recorded cases shows that it is inadvisable for any person to be further exposed to either of these insecticides if he has any of the following symptoms.

In the case of acute poisoning, the victim is usually irritable and frequently complains of nausea, vomiting and headaches. The last-mentioned are usually frontal and most severe in the mornings; analgesic drugs may give little or no relief. Continued absorption may cause fainting, muscle spasms, tremors and loss of weight. Other symptoms often present are dizziness, diplopia, loss of appetite, abnormal sweating, insomnia and personality changes. Little is generally found on physical examination, except perhaps muscular twitching and occasionally altered deep tendon reflexes.[6] Further absorption may cause convulsions and subsequent coma.

Persons who swallow more than 10 mg. per kg. of body weight frequently become acutely ill. Symptoms may appear within 30 minutes, and rarely, if ever, is the latent period longer than 10 to 12 hours. Many observers have commented that, owing to the difficulty in inducing doctors to report cases of poisoning, it is difficult to obtain reliable statistics as to the incidence of epileptic fits occurring in those people with prolonged exposure. In the case of dieldrin, percentages ranging from 47 to 100 have been quoted; in some instances seizures have occurred as late as 120 days after the last exposure.[4] In 1952, Spiotta and Winfeld[7] recorded details of an attempted suicide by drinking ". . . a 'Coca-Cola' bottle full of Aldrin mixture . . . this was equivalent to 1·8 gr. of concentrated Aldrin or 25·6 mg./kg. . . . 18 days after ingestion the initial electroencephalogram showed a basic 6 per sec. generalised slowing and 3 per sec. spike and wave discharges with a multiple spike component. Serial E.E.G.'s over five and a half months showed complete clearing of the abnormalities seen in the first tracing . . .".

Renal and degenerative liver changes may also occur, the former acutely; the latter are more likely to arise from chronic exposure.[11,12]

A previous report[8] has shown that animals given aldrin experimentally convert this insecticide to the epoxide, dieldrin, and that it is the latter compound which is stored in the fatty tissues of the animal.

Dieldrin has been detected in fat biopsy specimens subsequent to occupational exposure. For example, in February and March, 1958, a New Zealand farmer dusted approximately 34,500 sheep with 3% dieldrin solution; an additional 800 were similarly treated in August of the same year. His total exposure was about 18 hours. A fat biopsy specimen taken the next month contained from 5 to 7 p.p.m. of dieldrin. This farmer suffered from twitching of the arms and legs sufficiently severe to waken him at times.[9] Another person from the same country, the pilot of a Tiger Moth aircraft, was engaged in aerial weed control and insecticide spraying. During a period of six weeks, 17,000 gallons of a solution made up of one part of 15% dieldrin solution to 38 of water were sprayed; the pilot was drenched with this solution several times. About a month after cessation of spraying he developed symptoms similar to those of dieldrin poisoning; a fat biopsy specimen taken eight months later contained 1 p.p.m. of dieldrin.[10]

Clinical Record.

The patient, a man, aged 20 years, had worked as a labourer for a small manufacturing chemist for four years. As far as can be ascertained, he had not previously been significantly occupationally exposed to any insecticide; his main work consisted of keeping the factory clean and labelling tins, etc. His past medical history was irrelevant, except for an appendicectomy at the age of five years, and a motor-car accident eight years later. In this accident he sustained simple fractures of skull and jaw and compound fractures of both legs; he was in hospital for a period of four months, being unconscious for three days. During the next four years he complained of intermittent headaches, and as a result an electroencephalogram (Figure I) was taken. The report (Dr. L. Rail) reads as follows:

> . . . this record is characterised by a 9-10 c.p.s. alpha which blocks normally on visual attention. There are no significant changes on over breathing. OPINION. This record is within normal limits. There are no E.E.G. signs of brain damage.

The headaches subsequently gradually decreased in severity, and at the time of the aldrin episode the patient had been untroubled for four and a half years.

On the morning of June 29, 1959, the patient and a fellow worker were instructed to open some 500 large cases, each of which contained 10 individual five-pound cardboard packets of aldrin. Many of the latter had been damaged, and the patient's instructions were to empty these into

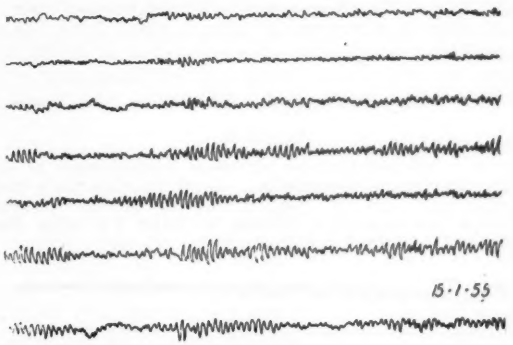

FIGURE I.

44-gallon drums and then, by means of a hand scoop, to repack the insecticide into new five-pound containers. There was no exhaust system to trap the dust and so prevent personal and atmospheric contamination. This work was carried out in the rear section of a room approximately 80 feet long, 20 feet wide and 14 feet high. Ventilation of the factory was by natural means, being dependent on a double door at the front, a smaller one at the rear and several windows in the sides of the building. When I visited the factory, there was no noticeable air movement. During the repacking there was quite a lot of spillage, and gross skin contamination was said to have occurred. The patient's wife stated that when her husband came home for tea, his face, hair and eyebrows were white with powder. He was not able to take a shower before leaving work, owing to the lack of suitable amenities. By the end of the day the overalls supplied by the firm were also heavily contaminated; gloves were not worn. Neither the patient nor his fellow worker used an anti-dust respirator; instead, each tied a handkerchief over his mouth.

By the end of the first day, 500 five-pound packets had been repacked. The next day, in order to speed things up, the manager detailed an additional three men to carry out similar duties within three or four yards of the patient. The newcomers all wore anti-dust respirators. By the end of the second day an additional 750 five-pound packets had been emptied and suitably repacked.

About 8 p.m. on the night of June 30 the patient was playing cards with his father when, according to his wife, "he started to make queer faces, and then went stiff and subsequently started to shake violently all over his body. He was also frothing at the mouth and rapidly became quite blue in colour". He apparently recovered consciousness in about three to five minutes, and complained of feeling dizzy and sick for the next one and a half hours. His doctor (Dr. R. Voss) saw him immediately afterwards, when "he was confused—the only abnormal signs were bilateral extensor plantar responses. Next morning, except for muscular stiffness, he felt well and his plantar responses were normal. His urine, heart, blood pressure and abdomen were all normal. . . ."

I examined the patient two days later; then the only abnormal physical signs were exaggerated knee jerks, especially the right. His hæmoglobin value, red and white cell counts and differential white cell counts were all

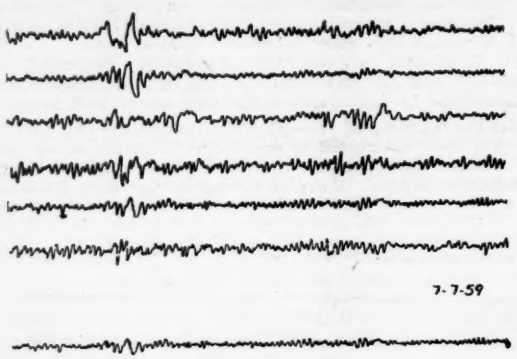

FIGURE II.

normal. Microscopic and chemical examination of his urine revealed no abnormality. Liver function tests were carried out, and the report was as follows: "Serum bilirubin not increased, Thymol turbidity 2·8 units, Zinc turbidity 5·9 units."

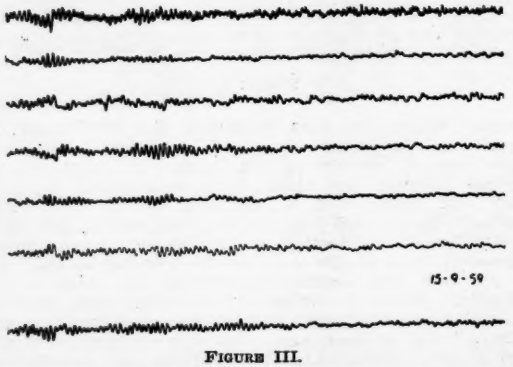

FIGURE III.

An electroencephalographic examination was made on July 7. This was reported on as follows (Dr. L. Rail):

> This record is characterized by a 10-11 c.p.s. alpha which blocks normally on visual attention. There are occasional bilateral 4-7 c.p.s. waves which appear in paroxysms and at random. Similar on overbreathing. No significant change on photic stimulation. No asymmetries or focal abnormalities.
>
> OPINION. This record shows occasional slow activity.

This abnormal electroencephalogram is not in any way specific for aldrin, but shows changes consistent with an encephalopathic condition due to a toxic substance. As such changes generally return to normal within a few weeks, the electroencephalographic examination was repeated on September 15. Dr. Rail commented as follows:

> This record is characterized by a 10-11 c.p.s. alpha which blocks normally on visual attention. 18-22 c.p.s. fast activity noted bilaterally. No significant changes on overbreathing or photic stimulation. No asymmetries or focal abnormalities.
>
> OPINION. This record is now within normal limits. This further confirms the diagnosis of Aldrin poisoning.

It may be relevant to recall that post-mortem examinations carried out on animals which have died as a result of experimental aldrin poisoning have revealed generalized vascular congestion with blood-vessel cuffing, severe ganglion-cell degeneration and eccentric hyperchromic nuclear staining of neurophagia.[7]

On July 14 a biopsy was carried out, and 3·3 grammes of fat were forwarded in chemically pure carbon tetrachloride to the Technical Development Laboratories, Communicable Disease Bureau of the U.S. Department of Health, Education and Welfare. Mr. C. Cueto[13] subsequently reported as follows:

> . . . using a diphenylamine-zinc chloride colorimetric method, 40 p.p.m. of Dieldrin detected. The phenylazide method showed no significant amounts of Aldrin present.

It is known that relapses have occurred after cessation of exposure to dieldrin, but none have so far been reported to occur similarly with aldrin. At the time of writing this report (April, 1960) the present patient felt well; he had suffered no further ill health.

Summary.

Subsequent to inhaling heavy concentrations of aldrin powder during two working days, a young man had a convulsive seizure. His electroencephalogram showed changes consistent with those caused by a toxic substance, and 40 p.p.m. of dieldrin were subsequently detected in his subcutaneous fat.

Acknowledgements.

I wish to thank Mr. Cipriano Cueto, junior, of the Communicable Disease Centre, Savannah, Georgia, U.S.A., for his courtesy and kindness in carrying out the fat analysis referred to in this article. In addition I wish to thank Dr. L. Rail and Dr. K. Voss for access to their clinical notes and for their professional opinions. Finally, I should like to thank Dr. C. Cummins, Director-General of Public Health of the N.S.W. Department of Public Health, for permission to publish this report.

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The Medical Journal of Australia

SATURDAY, OCTOBER 29, 1960.

THE VICTORIAN CANCER CONGRESS.

THE Victorian Cancer Congress, held in Melbourne from August 22 to 25, 1960, under the presidency of Sir Peter MacCallum, was the first of its kind in Australia. It was in fact an Australian, even an international, congress, but it was held in Melbourne, and Victorian enterprise, hard work and money went to make it the success that it was, so Victoria has every right to the credit for it. The body behind the Congress was the Anti-Cancer Council of Victoria, and in the immediate foreground was a committee led by Sir William Upjohn as chairman, with Professor M. R. Ewing as vice-chairman, Dr. E. V. Keogh as medical adviser, Mr. B. J. V. Ramsden as honorary treasurer and Dr. F. Douglas Stephens as honorary secretary.

A report of the Congress is published elsewhere in this issue (see page 706). Most of this report is taken up with a summarized account of the papers presented, which were in general of a high order. This fact was ensured—although in saying this we cast no reflection on the Australians who presented papers—by the presence of a group of notable visitors. They included the following: Professor R. A. Willis, a distinguished Australian who is now Emeritus Professor of Pathology in the University of Leeds; Dr. Peter Alexander, Dr. D. A. G. Galton, and Professor B. C. Koller, from the Chester Beatty Research Institute, London; Professor I. Berenblum of the Weizman Institute of Science, Rehovoth, Israel; Dr. F. Bielschowsky of the University of Otago Medical School, and Dr. Stephen Williams, from the Green Lane Hospital, Auckland, New Zealand; Dr. Jacob Furth of the Roswell Park Memorial Institute, Buffalo, New York, U.S.A.; Professor V. R. Khanolkar of the Indian Cancer Research Centre, Bombay, India; Professor J. A. Miller and Associate Professor Elizabeth C. Miller of the McArdle Laboratory for Cancer Research, Madison, Wisconsin, U.S.A.; Dr. E. L. Wynder of the Memorial Center for Cancer and Allied Diseases, New York, U.S.A.; Professor T. Yoshida of the University of Tokyo, Japan. A number of the papers contributed by these visitors have been made available and will be published in full in the Journal in due course. One outstanding feature of this Congress, the Scientific Exhibition, has received perforce only brief reference in our report, as it was essentially in the form of a visual display not lending itself to summary. It was, however, a remarkably fine presentation, leaving a striking impression of the amount of positive and productive work being done in Australia in the field of cancer research.

One question that naturally arose at the Congress was the future of the various Australian State cancer research organizations and the possibility of their coordination. It was widely discussed on an informal level, and some exploratory examination was made of the position. At the opening meeting Councillor W. J. Fitzpatrick, a layman and responsible citizen who has done much for cancer research and the cancer sufferer in Australia, referred to the possibility of the formation of an anti-cancer council on an Australia-wide level, and we know that a number of influential and informed people are pursuing this objective. Everyone will wish them success, provided that a formula can be devised which will ensure an effective use of resources on a Commonwealth level without any discouragement to the generous support being given by citizens on a State level, as well as a coordination of research which will still be acceptable to State bodies and to individual workers. This is not a simple matter, and it will probably not be settled in a hurry; indeed, it would be wise to hasten slowly. A worthwhile advance will have been made when Australian cancer research can speak with one voice, but only if it is a truly representative voice.

MEASLES-VIRUS VACCINE (ATTENUATED).

THE discovery by J. F. Enders, T. H. Weller and F. C. Robbins, reported in 1949,[1] that poliovirus would grow in cultures of non-neural tissues marked the beginning of a new era in virology, and it was most fitting that these three men should have been jointly awarded the Nobel Prize for Physiology and Medicine in 1954. Not only did this lead directly to the development of poliovirus vaccines, but it has resulted in the isolation of whole families of hitherto unknown viruses from cases of human disease, notably the ECHO viruses and the adenoviruses. There has emerged also a much deeper understanding of some of the common human infectious diseases, and notably of measles. Here again Enders has been responsible for the important pioneering discoveries, and much of the subsequent developmental work has been his also.

Claims have been made over many years that measles virus could be cultivated in tissue cultures and in the developing chick embryo. Usually these were erroneous, and the first successful cultivation of measles virus seems to have been that reported by H. Plotz in 1938[2] in chick embryo tissues, and by G. Rake and M. F. Shaffer in 1940[3] in the developing chick embryo. From the point of view of using a cultural technique for further study of the nature of a virus and the disease which it causes, both these methods suffered from the fact that no alteration was observed in the tissues, either macroscopically or microscopically. The presence of virus could be ascertained

[1] *Science*, 1949, 109: 85.
[2] *Bull. Acad. Méd. (Paris)*, 1938, 119: 598.
[3] *J. Immunol.*, 1940, 38: 177.

only by passing the culture fluid in monkeys or susceptible human beings. In 1954 Enders and Peebles[4] described the cultivation of measles virus in human post-nasal tissue grown in roller tubes, and subsequently a large variety of cell types have been shown to be susceptible. The notable feature about this work was the demonstration of distinctive cytopathic changes, so that titrations of virus and of neutralizing antibody could be made with the cultured cells themselves. Several interesting developments have followed. Firstly, measles virus has been shown to be related to two animal viruses, those of canine distemper and rinderpest of cattle. Secondly, observations have been made on the pathogenesis and the immune response in measles. And thirdly, an attenuated virus vaccine has been developed and subjected to preliminary trials in man.

The development and subsequent clinical trials of the measles virus vaccine have been reported in a series of eight papers published in a recent number of *The New England Journal of Medicine*.[5] They parallel and greatly extend investigations on measles vaccine carried out in the U.S.S.R. since 1956. After several early failures to adapt measles virus strains carried in human renal cells to grow in chick embryos, successful passage of the Edmonston strain was accomplished, and it was then adapted to grow in chick cells maintained with a synthetic medium. This led to the production of virus free from extraneous protein except for small amounts derived from chick-cell substrate. After it had been shown that this chick-adapted virus produced a good antibody response in monkeys, with no clinical signs of viræmia, and no evidence of multiplication in the central nervous system after intracerebral injection, limited clinical trials were undertaken in children. The first trials showed that the clinical response evoked by measles vaccine was moderate fever followed by mild rash, with an absence of toxicity. In contrast to natural measles infection, it proved impossible to detect viræmia. Subcutaneous injection proved the most satisfactory method of infection, and in no case was this followed by excretion of the virus via the respiratory tract or otherwise. No cases of contact infection of susceptible non-vaccinated children were reported, nor did the usual bacterial complications of natural measles develop. The incubation period after subcutaneous vaccination is three to five days shorter than in the natural disease, so that it is possible that vaccination would be a useful measure in the presence of an epidemic situation.

So far only 44 of the vaccinated children have been exposed to natural measles infection, but all of them proved resistant. Measles is such a common disease, and subclinical attacks are so rare, that further information on the degree of protection, and ultimately its duration, will accumulate much more rapidly than was the case with poliomyelitis. There are mild febrile reactions to measles vaccine, but these are almost universal in smallpox vaccination and constitute no contraindication for that procedure. There is, therefore, real promise that a safe and effective vaccine may soon be available. We look forward with interest to further reports of the degree and duration of the resistance to natural measles conferred by the new vaccine

[4] *Proc. Soc. exper. Biol. & Med.*, 1954, 80 : 277.
[5] *New Engl. J. Med.*, July 28, 1960.

Current Comment.

GLYCEROLIZED FROZEN BLOOD.

WITH the greatly increased demand for blood for transfusion, partly because of the development of apparatus for a variety of medical uses such as heart-lung oxygenators and kidney dialysers, methods for the storage of whole blood or red blood corpuscles for long periods are being intensively studied. If methods could be devised to enable blood to be stored, and still remain viable, for twelve months or more, it would be possible to stockpile blood in large amounts for emergency use, such as after nuclear attacks. It would also be extremely useful to be able to set up blood banks of rare types of blood. However, the technical difficulties to be overcome are very great. Freezing seems to be the obvious method, but the formation of ice crystals in the corpuscles must be avoided, otherwise the cells will break up. The finding that cells exposed to glycerol and other polyhydric alcohols could be frozen and thawed without significant damage opened up new fields for investigation. Erythrocytes could be preserved in this manner, but the fact that glycerol had to be removed before the erythrocytes could be injected into man introduced new complications. The glycerol itself is not toxic, but the introduction of glycerolized blood cells into an aqueous solution results in excessive swelling and rupture of the treated corpuscles, because water passes into the glycerolized cells faster than glycerol diffuses out. Methods have been devised to get rid of the glycerol, but it is difficult to maintain asepsis. Nevertheless, workers in many places are endeavouring to work out satisfactory methods for using glycerolization-freezing techniques. A group of six workers, led by L. L. Haynes,[1] at the United States Naval Hospital in Chelsea, Mass., under the joint supervision of the Department of Navy and Protein Foundation of Boston, Mass., have worked out a practical method for the long term preservation of human blood. They report that red blood cells have been glycerolized, frozen at −80° C. and stored up to 44 months, and then have been deglycerolized, reconstituted and successfully given to patients. The method involves the use of a very special fractionator for blood, the Cohn fractionator, developed by E. J. Cohn in 1951 for the separation of blood into its component parts. The fractionator contains a sterile centrifuge that operates under precise temperature control, but no other details are given as to its structure or mode of working. The glycerol concentration in the preserved cells was 40% to 50%. For ordinary use the thawed, deglycerolized red cells were mixed with a resuspension medium containing 5% albumin, sodium chloride, dextrose, potassium phosphate and distilled water. For reconstituted blood an amount of 200 ml. of original plasma was used per unit of red blood cells. Bacteriological control was maintained at every stage.

The use of the apparatus for hospital preparation has been found to be as satisfactory as on a laboratory scale. There have been very few technical failures, and the laboratory personnel used totalled only six for all work. The Naval Hospital now uses stored blood, and a good collection of rare types has been made. Studies were done with radio-chromate to determine the degree of survival of the treated corpuscles, and this varied in blood stored for periods of 1 month to 21 months from 82% to 95% of the cells. Most of the red blood cell loss was due to mechanical rather than hæmolytic loss and appears to have been independent of storage time.

Blood preserved in this way has been used for all types of patients needing blood transfusions. In all cases in which the blood has been used for volume replacement, red blood cells resuspended in 5% albumin menstruum, as mentioned earlier, have been adequate. For certain purposes the red cells are resuspended in original plasma. The over-all incidence of side reactions has been

[1] *J. Amer. med. Ass.*, 1960, 173 : 657 (August 13).

less than 0·5%. In some respects the stored blood is better than fresh blood for transfusion, for the washing process removes leucocytes, platelets and products of dead cells and reduces the risk of hepatitis. The operational costs have not been great and could be reduced by simplifying the apparatus. In other places other methods are being studied for the preservation of blood over long periods, and there is little doubt that even more satisfactory means will be devised in the near future which will greatly extend the use of blood transfusion.

CANCER OF THE LUNG.

A RECENTLY published symposium by the Thoracic Society of Great Britain has the clumsy title "The Present Position Relating to Cancer of the Lung", but it has some notable contributors, including A. Brian Taylor, Vernon Thompson, Russell Brock, C. Price Thomas, H. C. Nohl and Gwen Hilton.[1] George A. Mason introduces the subject with the observation that more than 20% of men and 5% of women who die of cancer have the growth in the lung. He states that the prognosis for small-cell cancer is so poor "that perhaps it should not be operated upon at all", and he draws attention to the high incidence of vascular involvement in peripheral adenocarcinomas and large cell cancers.

A. Brian Taylor presents a follow-up study of 8002 patients with lung cancer seen between 1937 and 1957. Of this total 4054 were seen between 1947 and 1954, and this series was especially studied for prognosis. Resection was performed in 678, and 21·7% were alive five or more years after operation. The operation mortality was 13·7%. By contrast, 91·6% of those who did not have the operation were dead within one year. Vernon Thompson presents a personal series of 399 operations, with a resection rate of 77% and an operative mortality of 5·8%. This covers a 15-year period (1941 to 1956). His five-year survival rate is 27·3%, and his ten-year survival rate is 16·6%. He has had no deaths from metastases after ten years, which corresponds with most surgeons' experience. But, like others, he has had survivors who developed a fresh primary cancer of the lung. Two patients are still alive eleven and five years after segmental resection, and another has survived eleven years after removal of a cerebral metastasis followed by resection of the primary growth of the lung. Russell Brock discusses his results with both radical and simple pneumonectomy; good surgeon as he is, he finds that there is time and place for both types of operation. C. Price Thomas deals with the operation of lobectomy with sleeve resection of part of the main bronchus; the object of this operation is to place the line of section well above the growth. It may be necessary to remove a segment of the pulmonary artery at the same time, especially on the left side.

H. C. Nohl, in a follow-up study from the London Chest Hospital, discusses some of the factors concerned with prognosis. For example, the size of the growth is important, because the larger the growth the greater the chance of lymph node and venous involvement. If the glandular involvement is limited to the intersegmental and interlobar nodes, the prognosis seems to be as good as it is without lymphatic invasion. But if mediastinal glands are invaded, the prognosis is uniformly bad. Involvement of the pulmonary vein is common, and the greater its extent the greater the lymph node invasion and the worse the outlook. Central growths have a higher incidence of vascular invasion than more peripheral growths. Nohl claims that this study makes it possible to give an individual prognosis, contrary to a statement made by John Borrie in his Hunterian lecture in 1952.

Gwen Hilton deals with the results of radiotherapy alone. There is general agreement about its palliative value in the relief of symptoms. Thirty-eight patients with operable lesions were treated by radiotherapy, and eight of them lived for more than five years; four of them had undifferentiated cancer, and four had squamous cancer. In six of the eight the growth was situated in the right lower lobe. Although pulmonary function is reduced by radiotherapy, the reduction is not as great as it is after pneumonectomy. These figures should prove a stimulus and challenge to other radiotherapists, as the results given are well above the average.

[1] *Thorax*, 1960, 15:1 (March).

"BANGUNGUT."

NEXT time a diagnosis is needed for the certification of the sudden and inexplicable death of a young man it may be an idea to consider "bangungut". It would be original and no less fanciful than the diagnoses sometimes used. "Bangungut" is a disease of which 20 to 30 cases are seen annually in Manila alone. It occurs in the Philippine Islands, mostly to Filipino males of between 30 and 40 years of age, and among Filipinos living in the Hawaiian Islands, but it has been reported amongst non-Filipinos in the Philippines. The name, though it suggests some gastro-intestinal disorder to our ears, in fact comes from the Tagalog *bangun* (to rise) and *ungul* (to moan). The patient goes to bed well after a normal Filipino meal, during the night moans, has nightmares, yells, coughs and may exude frothy fluid from the mouth, and dies in some minutes. Or he may be found dead in bed. The invariable mortality and the absence of milder cases add to the mystery of its ætiology.

G. E. Aponte,[1] writing on "The Enigma of 'Bangungut'," reviews the literature and discusses 11 cases seen in the last four years at the United States Naval Hospital at Guam. At post-mortem examination acute cardiac dilatation was seen, with pulmonary œdema and scattered subpleural areas of ecchymosis. The lungs were heavy and exuded copious amounts of sero-sanguineous fluid. The interesting changes were in the pancreas. In 5 of their 11 cases there was interstitial pancreatitis of mild to moderate severity. The pancreas was swollen and red. True necrotizing pancreatitis was not observed.

Theories as to cause there are, but no satisfactory answer. One possibility is the occurrence of a powerful vagus reflex mechanism due to gastric overdistension. More favoured is the presence of some toxic material in the fishes eaten, especially the *patis*, a sauce made from fish. Experiments in dogs confirm the presence of some toxic substance; but still unexplained is the fact that death from "bangungut" strikes at healthy males of a restricted age group and never anyone else who shared the same meal.

There must be a rich harvest of medical knowledge to be gained by studying the geographic idiosyncrasies of various diseases. Soon a good atlas will be a necessity in every medical library. Unhappily much information has been fascinating but enlightening. True, the tracing of various blood groups and of the abnormal hæmoglobins has provided ethnological clues, but the vast material on varying incidence of neoplastic disease or of atherosclerosis throughout the world has no agreed implication. Be that as it may, those who are anchored to their practices may still find an opportunity to indulge in some armchair globe-trotting. What of kuru, localized to an area in New Guinea, or the cases of motor neuron disease described in the islands about Guam? Then consider Sao Paulo. Why the high incidence of achalasia of the œsophagus in the Indians there? Or would you visit Ankara? From there you may investigate the outbreak recently reported by Schmid[2] of cutaneous porphyria in Turkey, traced to the fungicide hexachlorobenzene, which had been used to treat wheat intended for sowing but misdirected for human consumption. This is an interesting "break-through" in providing an exogenous causative factor in a disease which would appear usually to be an inborn error of metabolism.

[1] *Ann. intern. Med.*, 1960, 52:1258 (June).
[2] *New Engl. J. Med.*, 1960, 263:397 (August 25).

Abstracts from Medical Literature.

NEUROLOGY.

Temporal Lobe Epilepsy due to Small Focal Lesions.

M. A. FALCONER AND J. B. CAVANAGH (*Brain*, December, 1959) discuss clinico-pathological considerations of temporal lobe epilepsy due to small focal lesions. They point out that if cases due to large space-occupying lesions are excluded, in two-thirds of cases of intractable temporal lobe epilepsy submitted to operation the underlying pathological cause is a diffuse sclerosis, particularly of the mesial portion of the temporal lobe, that usually dates from infancy, while in the other one-third the condition is apparently due to small focal lesions of great pathological diversity. The authors have selected 23 patients with drug-resistant psychomotor seizures for study, all of whom at operation were found to have small focal lesions; these were small neoplasms in 13 cases, vascular malformations in two cases, and cortical scars in five cases. The 15 patients with neoplasm or vascular malformation all showed attacks of the psychomotor type—sudden confusion, with subsequent amnesia, usually commencing with a sensory aura, and often accompanied by purposeful but poorly coordinated movements, but without a convulsion. The auras were epigastric or cephalic sensations, *déjà vu*, strangeness or unfamiliarity, micropsia, taste or smell, visual hallucinations, fear and tinnitus. Only three of these patients had grand-mal seizures. The personality disturbance varied, i.e. aggressive outbursts, inadequate personality, paranoid or hysterical disturbances. The electroencephalograph studies showed ipsilateral spike-discharging foci in 14 patients, spike foci in the opposite temporal lobe in 5 patients, associated slow wave activity in 13 and reduced barbiturate fast activity at the ipsilateral sphenoidal-ear electrodes in 5. Post-operatively, epileptic activity disappeared from the records of 12 out of 15 patients. This improvement in the electroencephalogram paralleled the clinical improvement.

Epidemic Vertigo.

E. PEDERSEN (*Brain*, December, 1959) has reviewed the literature on epidemic vertigo and analysed 400 cases occurring in Denmark. The names of epidemic neurolabyrinthitis, vestibular neuronitis and acute labyrinthitis have often been given to this clinical syndrome. The author's cases occurred in 25 epidemics. He has shown that the condition is benign and that the patient eventually recovers completely. Gastro-intestinal symptoms, diarrhœa and vomiting were common in one group of cases, while in a second group fever and the signs of an upper respiratory tract infection occurred. The only definite neurological sign was a horizontal nystagmus and this was relatively uncommon. The author was unable to determine with certainty the site of the lesion responsible, and special investigations were of little help. He suggests that probably the second vestibular neuron is primarily involved, possibly in the brain stem. A virus infection seems the most probable cause, but no organism has ever been isolated. There is no specific treatment, but some patients have improved with the antihistamines. Some become depressed for a few weeks after the acute stage and require treatment. However, total recovery is the rule.

Observations on 500 Cases of Migraine and Allied Vascular Headache.

G. SELBY AND J. W. LANCE (*J. Neurol. Neurosurg. Psychiat.*, February, 1960) discuss some observations on 500 cases of migraine and allied vascular headaches. There were 300 females and 200 males; 90% of patients were less than 40 years old when the first attack occurred. Heredity and personality provided the common background. One-third had an allergic diathesis. A family history of epilepsy was elicited in 15% of patients. The average frequency of attacks was one to four a month. Physiological and environmental factors were found to be precipitating factors. The attacks persisted for less than a day in two-thirds of patients. The site of the headache could be hemicrania, holocrania, or mixed forms. Associated symptoms were nausea, vomiting, photophobia, visual disturbances, paræsthesiæ, "dizziness" and vertigo. An assessment of personality revealed obsessional trends, tenseness, hyperactivity and anxiety in about half the cases. Electroencephalograph records were normal in 70% of cases; the remaining patients showed abnormalities such as excessive slow activity, asymmetrical slow activity and, rarely, wave and spike paroxysms. Ergotamine tartrate benefited 80% of these patients. Histamine was given by intravenous infusion to 76 patients who appeared to have allergic disorders. In 48 cases this therapy reduced the frequency of the attacks by at least half.

Spontaneous Cerebellar Hæmorrhage.

W. MCKISSOCK, A. RICHARDSON AND L. WALSH (*Brain*, March, 1960) review 34 consecutive cases of spontaneous cerebellar hæmorrhage. Most cases occurred at ages of between 60 and 80 years, and hypertension was the presumed cause in the majority of cases. There was no initial loss of consciousness in 18 cases, and these patients complained of headache and vomiting. In the majority of cases the cerebro-spinal fluid was blood-stained. The wide variety of the clinica picture is stressed, from the ingravescent type, presenting with meningism, cerebellar and brain stem signs, to the frank type with loss of consciousness and rapid death. In those cases in which the presence of a subarachnoid hæmorrhage was established, bilateral carotid arteriography was performed, followed by vertebral angiography, but the presence of a cerebellar hæmatoma cannot be excluded by vertebral arteriography. Ventriculography was performed in most cases. Fourteen of these patients were submitted to craniotomy, nine of whom survived. The authors conclude that there are at least 20% of patients for whom probably nothing can be done. In this group the onset is sudden, the course rapid and progressive, ending in death in 24 to 48 hours; cerebellar symptoms usually cannot be elicited, cerebellar signs are absent and the hæmorrhage presents as a coma-producing cerebro-vascular accident with bleeding into the subarachnoid space. In this group the hæmorrhage has usually ruptured into the brain stem. The largest group have a sudden onset with headache, vomiting, vertigo and ataxia, followed by loss or impairment of consciousness. This group, the authors consider, is amenable to surgery if managed correctly and expeditiously.

The Motor End-Plate in Myasthenia Gravis.

V. MACDERMOTT (*Brain*, March, 1960) discusses the changes in the motor end-plate in myasthenia gravis. The literature concerning the histology of muscle in myasthenia gravis is reviewed. Eight cases of myasthenia gravis are discussed in which muscle biopsy was performed, using the intravital methylene-blue technique in addition to routine stains. In nearly all cases the muscle selected was not clinically fatigable or weak, and there was no marked histological abnormality of the muscle when stained by routine methods. Most of the cases had normal electromyographic findings. The response to the decamethonium and "Tensilon" test was characteristic of myasthenia gravis in all the cases selected. In the sections stained with methylene-blue it was found there was considerable abnormality both of the distal nerve fibres and of the motor end-plates. The presence of abnormal end-plates is noted and the author describes an unusual pattern of distal nerve branching. It is suggested that the defect in myasthenia gravis is a primary neural one.

PSYCHIATRY.

Lysergic Acid Diethylamide as a Facilitating Agent in Psychotherapy.

A. L. CHANDLER AND M. A. HARTMAN (*A.M.A. Arch. Gen. Psychiat.*, March, 1960) report the treatment of 110 private patients who were given lysergic acid diethylamide (LSD-25) to facilitate psychotherapy. The sessions averaged four to four and a half hours each, and the authors comment that the patients require very careful follow-up observation and supervision. One of their patients committed suicide after treatment, but it is possible that other factors may have been responsible. Another patient continued in a psychotic state for one day after the treatment but subsequently settled down. No other serious reactions occurred in the authors' series, which included 44 cases of psychoneuroses, 25 of personality disorders, and 22 of sociopathic disorders (including 17 alcoholics or drug addicts). The authors claim that LSD-25 produces great intensification in the level of affectivity during the session, and that resistance to communicating transference feelings are reduced. The broadening of the spectrum of conscious awareness makes for the greater availability of early memories

in nearly all the patients. The drug enabled the authors to work with patients who were otherwise unresponsive to psychotherapy.

Motivational Patterns in Patients Seeking Elective Plastic Surgery.

E. MEYER *et alii* (*Psychosom. Med.*, May-June, 1960) have studied a group of 30 consecutive women patients who attended a plastic surgeon for rhinoplasty. Taped recorded psychiatric interviews were arranged prior to operation, and post-operative follow-up interviews were conducted. The ages of the patients ranged from 14 to 43 years, and in all of them a self-consciousness and preoccupation with the nose as ugly or inappropriate to the rest of the face dated from the period of adolescence. The authors consider that the motivations for seeking rhinoplasty varied with the age and life situation of the patient. These included: (*a*) cultural conflicts and the wish to avoid being stereotyped as alien (9 of the 11 adolescent patients were Jewish); (*b*) the presence of ambivalent parental identifications resulting in attitudes that are particularly restrictive in the area of expression of feminine and sexual attractiveness; (*c*) in older patients, the frequent presence of active interpersonal stress threatening the patient with depression. The authors regard the problems of adolescence as crucial in establishing the defensive use of feelings of deformity of the nose in an attempt to master conflicts. They believe that the operation functions symbolically as a disavowal of the restrictive aspects of maternal identifications. Prior to operation none of the patients or their parents had any record of significant psychiatric illness; however, three suffered from psychotic disorders in the immediate post-operative period.

Manic-Depressive Psychosis in Childhood.

J. ANTHONY AND P. SCOTT (*J. Child Psychol. Psychiat.*, January, 1960) review the literature on manic-depressive psychosis in childhood, and illustrate five different points of view regarding this occurrence and the nature of its manifestation. These are: (i) It is a psychodynamic entity, recognizable in earliest infancy and merging with normal development. (ii) It is a clinical phenomenon of early childhood. (iii) It is a clinical entity in itself, belonging to late childhood. (iv) Manic depression in childhood is an "early onset" variant of the adult illness. The reason for the early onset may be heavy genetic loading and intense environmental experience. (v) It exists as a simple amplification of a cyclothymic tendency, the emotional swings being largely unaffected by environmental conditions. The authors then report one case in detail and through the medium of this case attempt to reconcile many of these opposing points of view. The patient, predisposed by a double genetic loading, became manic at the age of 12 years when his father died and a brother was adopted. The authors maintain that owing to environmental handicaps this boy indulged throughout childhood in compensatory phantasies, and that the traumatic events extraverted his psychosis, altering his "flight into phantasy" into a "flight into reality". They believe that the occurrence of manic depression in early childhood as a clinical phenomenon is yet to be demonstrated.

Early, Prolonged Separation and Emotional Maladjustment.

M. L. KELLMER PRINGLE AND V. BOSSIO (*J. Child Psychol. Psychiat.*, January, 1960) state that in a previous study they found that 70% of the children reared in a Birmingham institution were considered to be unstable. In the present investigation, 11 "severely maladjusted" and five notably "stable" children from this group were studied in detail. The assessment of stability was based on the Bristol Social Adjustment Guides (completed by the house staff and by the class teachers), the results from a Ravens Controlled Projection Test, and clinical observations made by the investigators throughout the individual testing and interviewing of each child. Both of these groups had been separated from their mothers before the age of five years, and had continued to live apart from their parents for more than half of their lives. It was found that in the stable group separation appeared to have been caused by unfortunate circumstances rather than by rejection of the children, and their mothers kept in touch with them. The main difference in the two groups was that the maladjusted children were psychologically deprived, while the stable group was deprived of family life and physically separated but nevertheless loved and cherished by adults who were important to them. The authors conclude that their evidence suggests that the child who is rejected very early in life and remains unwanted is likely to become insecure, maladjusted and educationally backward. The practical implication of their study lies in the need to ensure that every child in institutional care has the opportunity to make a stable relationship with an adult in the outside world.

Critical Ages for Maternal Bereavement in Psychoneuroses.

H. BARRY, JR, AND E. LINDEMANN (*Psychosom. Med.*, May-June, 1960) state that there is some agreement that loss of a parent during childhood may result in immediate emotional disturbance, but that whether childhood bereavement can contribute to neurosis in later life has remained controversial. In the present study they attempt to clarify this problem and find that the death of the mother before a child is five years old occurred more frequently in a series of 947 neurotic patients than in the total population, and that the difference is statistically significant (0·01 level of confidence). The impact of maternal death was most pronounced in early childhood and in female patients. Girls under the age of three years were particularly vulnerable. Death of the father falls into a pattern which is more nearly like that found in the general population. The authors comment that although separation from parents for other reasons appears to parallel deprivation due to death, the term "broken homes" should be replaced by more specific descriptive categories.

PHYSICAL MEDICINE.

Judgement of the Median Plane in Hemiplegia.

H. G. BIRCH *et alii* (*Arch. phys. Med.*, February, 1960) examined a group of hemiplegic patients and control subjects in a task involving the perception of the median plane under dark and light conditions. Under dark conditions, the total hemiplegic group showed significantly larger median plane alterations than did the control group. Both the right hemiplegic and the left hemiplegic groups perceived the median plane to be significantly displaced to the affected side of the body. Under light conditions, median plane alterations were much reduced, but the hemiplegic group still showed significantly greater errors than did the control group. The results are discussed in connexion with the alteration in the mechanisms of median plane perception in hemiplegia.

A Modified Coaxial Electrode for Electromyography.

R. O. BECKER AND J. T. CHAMBERLIN (*Arch. phys. Med.*, April, 1960), from the Department of Surgery, State University of New York, describe a modification of the standard coaxial electrode, and present an investigation of its electrical parameters. They state that this type of probe has been in use for two years, and has been found to offer advantages—for example, reproducibility of results, complete coaxial shielding throughout, durability and ease of handling; cold sterilization is easily accomplished and efficient, and manufacture is easy. The design produces an exceptionally convenient and durable electrode, and eliminates the variables produced by frequent replacement of the standard type.

Meprobamate in the Treatment of Cerebral Palsy.

H. M. STERLING (*Arch. phys. Med.*, May, 1960) states that a number of clinical studies have been performed to assess the effect of meprobamate on the motor behaviour of children with cerebral palsy. He states that it is apparent from the results that a method of objective observation of the influence of drugs on such patients is available, in spite of the differences shown in maturity, skill and motor handicap and between successive periods of time for each child, as well as the more obvious differences between children. In this way subjective error, effect of learning and influence of other extraneous factors are minimized. Meprobamate produced no effect in doses of 100 to 200 mg. three times a day for periods up to a month, when compared with pre-medication and post-medication performance of four children with spasticity due to brain damage tested twice a week for eight months. One child, with mixed "tension athetosis" and spasticity, performed better during this study when he received the drug, although during a previous study he showed no change. Side reactions were no more frequent during the use of the drug than during the use of a placebo.

Congresses.

VICTORIAN CANCER CONGRESS.

THE Victorian Cancer Congress was held in Melbourne from August 22 to 25, 1960, under the auspices of the Anti-Cancer Council of Victoria. The President of the conference was SIR PETER MACCALLUM.

OFFICIAL OPENING.

The Congress was officially opened by the Premier of Victoria, the Honourable H. P. Bolte, in the Melbourne Town Hall on the evening of Monday, August 22. During the ceremony the President of the Congress, Sir Peter MacCallum, paid a tribute to the generous response that the people of Victoria had made to the appeal for cancer research. Councillor W. J. Kilpatrick, Chairman of Appeals of the Anti-Cancer Council of Victoria, referred to the possibility of the formation of a federal anti-cancer council to coordinate the work being done by separate bodies in the individual States. Professor V. R. Khanolkar, Vice-Chancellor of the University of Bombay and Director of the Indian Cancer Research Centre, Bombay, spoke of the work of the International Cancer Council. At the conclusion of the ceremony the President of the Victorian Branch of the British Medical Association, Dr. H. G. Judkins, presented the Crawford Mollison Prize to Emeritus Professor R. A. Willis for his recent publication entitled "The Borderline of Embryology and Pathology".

SCIENTIFIC PROGRAMME.

Carcinogenesis.

Significance of Experimental Tumours for Human Tumour Causation.

PROFESSOR R. A. WILLIS (Great Britain) presented a survey of the experimental results with the several classes of chemical and other carcinogenic agents, with the special object of focusing attention on the correspondence or non-correspondence of those results with what was known or suspected of tumour causation in man. He said that many chemical substances and other agents were known which had been proved to be potent carcinogens in animals but which had not been incriminated as causing any tumours in man. It was also possible to induce tumours experimentally by introducing carcinogens directly into tissues to which they could have no direct access in man. He discussed the significance of such experimental results and the information that they might be expected to give about the undiscovered causes of human tumours. This paper will be published in full in a later issue of the Journal.

Mechanism of Action of Chemical Carcinogens.

PROFESSOR JAMES A. MILLER (U.S.A.) discussed current concepts of the mechanism of action of chemical carcinogens. He said that many diverse chemicals were known which could induce tumours in experimental animals and in man. A high percentage of those chemical carcinogens were found among the polycyclic aromatic hydrocarbons and the aromatic amines. Such carcinogens had been used in most of the studies from which many of the ideas on chemical carcinogenesis had been derived. Unfortunately, progress in cancer research had not reached a stage that would permit the essential reactions involved in the induction and maintenance of any malignant state to be described aptly on a molecular level in detailed biochemical and biophysical terms. Professor Miller said that it was the purpose of his paper to discuss various theories of chemical carcinogenesis and to evaluate them in terms of current knowledge of carcinogens and metabolism. In general the theories concerned either the deletion of factors required for control of growth or the addition of factors which upset homœostatic mechanisms. In some cases additions and deletions might be different aspects of the same process, so that the gain or loss of one factor might lead to the respective gain or loss of still other factors in the chain of events. Many of those factors, or at least the ultimate substances containing the relevant information, were considered to be specific nucleic acids, proteins and combinations thereof; among those would be latent viruses and other self-reproducing particles. It should be emphasized that at present there was no compelling evidence for a unitary theory of carcinogenesis. The mechanisms involved in the genesis of malignant cells might vary greatly for different kinds of carcinogens and different tissues.

Hormonal Aspects of Carcinogenesis.

DR. F. BIELSCHOWSKY (New Zealand) presented a paper on the hormonal aspects of carcinogenesis. He discussed first the problem whether hormones were carcinogens and showed, with the experimental tumours of thyroid and pituitary as models, that hypersecretion of hormones as well as a hormonal deficiency could lead to neoplasia. As in the case of chemical carcinogenesis, the final result of a chronic disturbance in hormonal homœostasis could be a neoplasm possessing all the characteristics of malignancy. However, the pathogenesis of the tumours induced by an endocrine imbalance appeared to differ from that of the chemically induced tumours. The sequence (progressive diffuse hyperplasia, nodular hyperplasia, metastasizing tumour), as well as the dependence on a time factor in the case of tumours of endocrine glands and their target organs, was illustrated. Dr. Bielschowsky then went on to show that hormones frequently played a permissive role in the development of tumours induced by chemical carcinogens or viruses, and that they often determined the response of non-endocrine tissues, such as the liver, to potent carcinogenic agents.

Cancer Hazards in Everyday Life.

PROFESSOR W. E. DAVIES (Melbourne) discussed cancer hazards in everyday life. He said that the problem was the frequent contact with small quantities of carcinogens, especially certain polycyclic aromatic hydrocarbons, over long periods. Polycyclic aromatic hydrocarbons were formed by heating food to temperatures attainable in kitchens. It was now found that the heating of starch in a steel vessel at 370° to 390° C. rapidly produced traces of the carcinogen benzpyrine. Also cholesterol more slowly yielded over 1% of polycyclic aromatic hydrocarbons. The "char" of cakes contained benzpyrine. In addition there was contamination of foods, as bought, by carcinogens introduced in food preparation (e.g., smoked meats) or by horticultural spraying. Polycyclic aromatic hydrocarbons also occurred in the products of incomplete combustion, e.g., some carbon blacks, exhausts, dust from abraded tyres and tarred roads, tars, such as tobacco tar, and smoke and smog.

Chromosomes of Malignant Cells.

PROFESSOR P. C. KOLLER (Great Britain) said that since 1950, as the result of the use of improved cytological techniques, a great amount of information had been accumulated about chromosome constitution and behaviour in experimental tumours. It had been established that the chromosome pattern often differed from that of the normal cell, and that the cell population of ascites tumours was usually heterogeneous, being composed of several cell variants, differing in their chromosome patterns. In primary neoplasms chromosome polymorphism might occur, but recent findings strongly indicated that it was a secondary phenomenon and not directly related to carcinogenesis. Chromosome polymorphism was found to be of importance in tumour progression. The implication of chromosome polymorphism was discussed in relation to carcinogenesis, tumour progression and treatment.

DPN and TPN Synthesis in Relation to Malignancy.

PROFESSOR R. K. MORTON (South Australia) presented a paper by himself and M. R. Atkinson on DPN and TPN synthesis in relation to malignancy. He said that, as compared with corresponding adult normal tissues, tumours and fœtal tissues had much less of essential diphosphopyridine nucleotides (DPN) and triphosphopyridine nucleotides (TPN). A low content of pyridine nucleotides in epithelial tissues was thus negatively correlated with the rate of cell division and the number of mitoses. In animal tissues, synthesis of the DPN and TPN from the vitamin nyacin (nicotinic acid) involved several enzymes, of which one (DPN-pyrophosphorylase) occurred exclusively in the nucleus. The DPN-pyrophosphorylase activity was much lower in tumours and fœtal tissues than in corresponding normal adult tissues, and thus might account for the low pyridine nuclear-type content and the consequent high rate of cell division in tumours. It had been found that DPN-pyrophosphorylase purified over 5000-fold from pig-liver nuclei had about three times the affinity for nicotinamide mononucleotide as for the alternative substrate nicotinic acid mononucleotide. Administration of nicotinamide increased the tissue pyridine nucleotides and thus reduced mitoses in regenerating liver, in onion root tip and in fertilized eggs, and also prevented malignant change when mouse epidermis was treated with methyl-cholanthrene. It had been further found that purified DPN-pyrophosphorylase was strongly inhibited by cytotoxic ethyleneimines such as TEM. The cytotoxic effects of Bayer E-39 on tumours was antagonized

by nicotinamide. Thus the tumour-inhibiting effects of ethyleneimines appeared to be due to interference in tumour cell nuclei. Those results were in accord with the hypothesis propounded by Professor Morton that the enzymic aberration in pyridine nucleotide synthesis in malignant cells represented an important site for selective chemical control of tumours.

Enzymes of Red Cells in Malignancy.

MR. I. C. PARSONS (Victoria) said that patients with Hodgkin's disease frequently suffered from an unusual anæmia, consisting of abnormalities of iron utilization and storage, together with a shortened red-cell life span, as shown by radiotracer studies. To investigate the latter process, a study had been commenced of the red cell enzymes of patients with Hodgkin's disease to determine if intrinsic defects were present. Adenine and pyridine nucleotides were not found to be decreased in amounts. However, the average glucose-6-phosphate dehydrogenase level was found to be higher than normal; such findings previously had been described only during reticular cytosis. As the reticulocyte counts of the patients concerned were normal, a possible explanation of the discrepancy could be premature senescence of the erythrocytes. Thus the effect of removing older cells with low glucose-6-phosphate dehydrogenase levels earlier than normal would be to enrich the remaining cells with those having higher than normal average enzyme level. The cause of the aging was unknown, but Price and Greenfield had suggested that such a finite shortening of life span might be caused by extrinsic toxic substances; possibly those could inhibit critical enzymes. Mr. Parsons described experiments to verify the hypothesis by determination of such enzymes after red cell fractionations.

Leukæmogenesis in Mice: Adrenal Cortical Function.

DR. D. METCALF (Victoria) said that as part of a study of the factors influencing lymphoid cells during the development of spontaneous lymphoid leukæmia, the function of the adrenal cortex had been investigated. A comparative study had been made between the pre-leukæmic AKR mice and normal C3H mice of the same age and sex. Thymus weight was found to be the most sensitive index of adrenal corticosteroid action. At all ages, after three weeks, AKR mice showed relative thymus hyperplasia, compared with C3H mice. Adrenalectomy resulted in lymphoid hyperplasia in C3H mice, but had no effect on lymphoid organ weights in AKR mice. AKR mice were more sensitive than C3H mice to the lymphocytolytic effects of injected cortisone. A single injection of ACTH produced lymphoid atrophy in C3H mice but had no such effect on AKR mice. Multiple injections of ACTH in AKR mice produced slight lymphoid atrophy. It was concluded that the adrenal cortex was hypofunctional with respect to production of lymphocytolytic corticosteroids in AKR mice during leukæmogenesis. The adrenal hypofunction probably constituted an accessory factor in the ætiological complex causing lymphoid leukæmia in AKR mice and could encourage the emergence of leukæmic cells evoked by the primary ætiological agent.

Fluorescein-Globulin Staining of Tissues.

DR. C. J. LOUIS (Victoria), in a paper on fluorescein-globulin staining of tissues, said that the fluorescein-globulin stain had been used initially as a histoserological stain to show that the cells of rat hepatoma had lost their "organ specific antigens". The normal liver cells which necessarily contained their "organ-specific antigens" reacted with the stain and thus emitted a bright green fluorescence, whereas the cells of rat hepatoma failed to do so. That the reaction was not an antibody-antigen phenomenon was shown by the observation that identical results could be obtained by using (*a*) normal rabbit globulin, (*b*) rabbit globulin, (*c*) rabbit albumin, (*d*) serum protein fractions from other animals and even birds, and finally (*e*) egg albumen. In view of those results an alternative explanation was sought. Since anion-cation complexes were readily formed in mixtures of proteins, the formation of such salt-like complexes between "stain globulin" and cytoplasmic proteins could account for the staining reaction. Dr. Louis went on to say that the method of study referred to had been employed in a wide variety of tumours and tissues in both man and animals and, in particular, in series of carcinomata of the colon, breast, skin and uterus, in leukæmias in man and animal, and in thyroid gland and cells in tissue culture. In all cases differential staining was observed between malignant cells and their normal counterparts. Furthermore, in some cases in which it was clear that malignancy was going to develop, areas of loss or diminution of staining were formed.

Histochemical Demonstration of Nucleic Acids.

DR. D. W. MENZIES (Victoria) discussed methods of staining nucleic acids in tissue sections. In addition to the standard methods, he made reference to his own researches on differential metachromasia and red-blue combinations, with basic fuchsin, toluidin blue and cresyl blue.

New Names in Tumour Terminology.

PROFESSOR R. A. WILLIS (Great Britain) presented a paper with the title "New Names in Tumour Terminology'. He discussed some new names which had been introduced into tumour terminology of recent years and some old ones which had been resuscitated, and presented an assessment of their merits and demerits, especially their validity on histogenetic grounds. This paper will be published in the Journal at a later date.

Metabolic Fate and Carcinogenicity of 2-Acetylaminofluorene.

ASSOCIATE PROFESSOR ELIZABETH C. MILLER (U.S.A.) said that 2-acetylaminofluorene was a carcinogen of particular interest, since it had a high activity which was manifested in a number of species and tissues. Investigations by the Millers and by Morris and his associates had outlined the major structural requirements of the molecule for carcinogenic activity, and had shown that those requirements were less stringent for mammary gland, ear duct and small intestinal epithelium than for the liver of the rat. The in-vivo metabolism of 2-acetylaminofluorene had been extensively investigated by the Weisburgers and Morris, who had demonstrated the excretion of conjugates of six phenolic derivatives (1-, 3-, 5-, 6-, 7-, and 8-hydroxy-2-acetyl-aminofluorene) in the urine of rats. Studies by Gutmann and his colleagues, and in the Millers' laboratory, had shown that a TPNH-dependent oxygenase in the liver microsomes was the major source of the phenolic derivatives. Recent data from the Millers' laboratory had revealed the presence of another metabolite, *N*-hydroxy-2-acetyl aminofluorene, in the urine of rats fed the carcinogen continuously. That metabolite was excreted in increasing amounts as the feeding of the carcinogen continued; at 18 weeks it accounted for about 15% of the dose. The present data suggested that the new derivative might be an important intermediate in carcinogenesis. Thus, the excretion of *N*-hydroxy-2-acetylaminofluorene was low in the urine of animals protected from tumour formation. Furthermore, when injected intraperitoneally into rats, the *N*-hydroxy derivative caused much more extensive liver damage than an equimolar amount of 2-acetylfluorene.

Mechanism of Cancer Induction by Impermeable Films.

DR. PETER ALEXANDER (Great Britain) presented a paper, prepared in conjunction with the late E. C. Horning and T. L. Braithwaite, on the mechanism of cancer induction by impermeable films. He said that the Oppenheimers had discovered ten years previously that impermeable films when embedded subcutaneously induced cancer. Detailed work from the same laboratories had shown that the initial stimulus did not involve a chemical reaction with the film but that the carcinogenic action must be attributed to a physical factor. The authors of the paper had shown that the incidence of tumours was very dependent on the size of the film. Recent experiments showed that, while whole-body X-irradiation did not influence the carcinogenicity of cellulose films in rats, it was greatly reduced by the administration of stilbœstrol. Examination of serial sections and the preparation of radiographic arteriographs and venographs lent support to the view that the tissue surrounding the plastic film was badly vascularized and might be anoxic. The nature of the connective tissues surrounding the film in stilbœstrol-treated animals differed in some respects from that in ordinary rats, and that might be a factor in reducing the number of tumours produced.

Antigenicity of Malignant Tissue.

DR. SAUL WIENER (Victoria) said that the antigenic properties of extracts prepared from malignant and normal areas of the same tissue or organ removed at operation had been compared by means of the Schultz-Dale technique. Different extracts had been injected with an adjuvant into guinea pigs. At varying periods of time thereafter, the uteri of those animals had been first desensitized with normal human plasma and homologous normal tissue extracts and then exposed to the homologous cancer extract. Evidence was presented to suggest the presence of one or more antigens in certain tissues which had become malignant and their absence from normal tissue of the same organ. An

attempt was also made to demonstrate the presence of those abnormal antigens in the sera of patients suffering from carcinoma. The sensitivity and limitations of the Schultz-Dale technique for studying mixtures of related antigens were discussed.

Dimethyl Nitrosamine Carcinogenesis.

Associate Professor G. S. Christie (Victoria) said that dimethyl nitrosamine, in addition to possessing acute hepatotoxic action on a variety of mammals, was a reliable liver carcinogen for rats. When the material was mixed with a diet in the concentration of 75 p.p.m., hepatomata developed between the 150th and 250th days. During the first three months after feeding was started with dimethyl nitrosamine, there was little alteration in the appearance of the liver. Thereafter its size gradually decreased, and numerous pale nodules appeared in the substance. Progressive cytological aberration, increasing nuclear polyploidy and islands of staining failure with fluorescein developed. The primary tumours were often hæmorrhagic, but the pulmonary metastases, which were relatively common, were less prone to bleeding. In the better differentiated areas, the tumour cells usually resembled liver cells rather than bile duct epithelium. In his paper Professor Christie presented the pathological findings and the results of metabolic studies on the acute toxic process.

Canine Ovarian Tumours Following Stilbœstrol Administration.

Miss N. G. Jabara (Victoria) said that a group of eight dogs had been treated by repeated injection of depot stilbœstrol over a period up to 19 months. All animals at death had shown the presence of pathological changes in the ovaries. In one case the lesion had been classified as hyperplasia; in the other seven the lesions were regarded as neoplasms because of invasion. In three of those, metastases to other parts of the peritoneal sac were found. The lesion consisted of proliferation of follicular epithelium and of the serosal surface which became highly papillary. Downgrowth of cell cords and gland-like crypts penetrated the ovarian stroma. A variety of types of differentiation occurred in the cell masses. In her paper Miss Jabara presented and discussed the pathological findings.

Cancer in the Community.

Oral Cancer in India.

Professor B. R. Khanolkar (India) discussed the occurrence of oral cancer in India and its relation to certain habits. He said that most people interested in the study of cancer wanted to find out how cancer was caused. It was not possible to determine the cause of most cancers arising spontaneously in man, but there were some human cancers occurring in India which were associated with certain habits and usages. As an example, certain types of oral cancer were described, and it was presumed that particular habits could be considered to bear a probable causative relationship to their occurrence. The cancers referred to were the lower lip cancer, with its relationship to munching a preparation of tobacco powder, cancer of the cheek and chewing tobacco twist, cancer of the palate and inverted smoking of the cigar, and cancer of the base of the tongue and smoking "beidi". Professor Khanolkar also suggested that avoidance of those habits might prevent the appearance of the cancers described.

Public Attitudes Relevant to Cancer Education.

Dr. Godfrey Gardner (Victoria) said that research in Melbourne was attempting to investigate the level of knowledge of cancer in the community, the channels through which that knowledge reached the public, and the various attitudes existing towards the treatment of cancer. Whether people who had cancer, or thought that they might have it, sought medical advice would depend on such things as (a) their ability to recognize the possibility of symptoms, (b) their beliefs about the possibility of cure, and (c) their beliefs about the nature of treatment. Fear of cancer was very real, and the question must be asked whether attempts to educate the public would increase or decrease their willingness to seek treatment if necessary. The method of investigation was to have very extensive interviews with a small sample rather than a public opinion poll type of inquiry with a wide coverage of the public. By that means it was hoped to obtain more than superficial "respectable" answers, and to obtain deeper insight into some of the resistances which were likely to be encountered in a cancer education programme. Dr. Gardner reported the results that had been obtained so far, and discussed questions about the future scope of such research.

Cancer Films.

Mr. R. J. Thomson and Mr. Newman Rosenthal (Victoria) presented the results of a critical survey of cancer films carried out by the Department of Audio-Visual Aids in the University of Melbourne. The project had been undertaken for the Anti-Cancer Council of Victoria during the latter part of 1959 and during 1960, and was based on the reaction of audiences to three particular films designed to educate the public on cancer. On the basis of the findings from the project the following recommendations were made as to the production and presentation of public education films on the subject of early cancer detection: (i) The emphasis should be on an objective, "documentary" style of presentation. (ii) Anxiety should be kept carefully controlled by the provision of reassurances, preferaby in the form of simply phrased information on what action to take and what help might be expected from the medical profession (treatment, information, etc.) upon the detection of a possible cancer symptom. (iii) The nature of the disease should be stated, as also should the significance of metastasis, after which the factual emphasis should be on symptom recognition. (iv) Audio-visual teaching techniques should be exploited to the full. (v) The use of statistics should not be overdone. (vi) The "impersonal" narrator technique should be preferred to having either a patient or a doctor act as a narrator; if the technique was temporarily varied in the course of the film, a doctor and/or patients should speak for themselves instead of bringing the narrator before the cameras (especially not with a personal "sob story"). (vii) The presentation should be "sign posted" and rounded up at the finish with a not too sketchy summary; "flashback" techniques should be used in the summary, but the emphasis should remain one of objective restraint. (viii) An ideal film would be 12 to 15 minutes in length.

During the discussion the three films were screened.

Voluntary Community Effort in the Field of Cancer.

Councillor W. J. Kilpatrick (Victoria), in a discussion on voluntary community effort in the field of cancer, said that most citizens of a civilized community had an active desire to contribute to the world-wide effort directed towards the conquest of cancer. It was the reponsibility of organizations concerned with anti-cancer work to utilize the goodwill of the community to its best advantage. In this regard he discussed the experience of Victoria in a recent campaign for community cooperation.

Social Welfare of Cancer Patients in Victoria.

Mrs. Beryl B. Thomas (Victoria) discussed the social welfare of cancer patients in Victoria. She outlined the needs, both common and particular, of cancer patients in Victoria, and discussed and evaluated the methods adopted to meet them. She made particular reference to the scheme of subsidizing private hospital care for patients in the terminal stages of the illness. A description was given of the organization of the patient-care programme in rural areas, and reference was made to some of the difficulties inherent in that organization. Mrs. Thomas made it clear that social service to cancer patients could be effective fully only with the cooperation of medical practitioners.

What Should the Patient Be Told?

Sir William Upjohn (Victoria) discussed the question: "What should the patient be told?" He said that the guiding principle was to tell the patient that concerning diagnosis, treatment and prognosis which would be of the most ultimate benefit to him. Every patient with cancer or suspected cancer presented an individual problem. The degree of certainty of diagnosis varied widely. Even after biopsy and microscopic examination of the tumour some uncertainty might remain. In every case sufficient information should be given for the patient to understand the advice offered for treatment, and whether that was designed for possible cure or only alleviation. In cancer, prognosis concerning length of life was always uncertain, but in certain circumstances it might be necessary to make the best possible prediction.

Palliative Treatment of Advanced Cancer.

Mr. Victor Stone (Victoria) discussed the palliative treatment of advanced cancer. He made a plea for a new conception of the management of the patient with advanced cancer and described a practical plan that should be of great help to the patient, his doctors and all those concerned in his welfare. The basis of the plan was that the patient remained at home as much as possible while receiving all the benefits of modern medical treatment, such as surgery, deep X-ray therapy and chemotherapy. The doctor should

play an important part in the management of the patient. His role and that of the cancer specialist were clearly defined. Full details of the plan covering the medical control and the home management were given. Mr. Stone stressed the importance of obtaining the complete confidence and cooperation of the patient and indicated the means of maintaining the patient's general strength and morale. Great importance was attached to full relief of pain by a definite method which must be completely effective. In conclusion Mr. Stone discussed the question of euthanasia and gave reasons for strongly condemning it.

Dietetic Care of Cancer Patients.

MISS CAROLYN N. TURNER (Victoria) discussed the dietetic care of cancer patients. She said that cachexia had been regarded as an inevitable part of malignant disease. In many cases it was a state of malnutrition due to some factor interfering with the patient's normal intake and utilization of food. Factors which might be responsible for such a state of malnutrition were numerous and included anorexia, mouth and throat lesions, radiation reactions, mechanical obstruction and defective absorption. The effect of those factors could be diminished by suitable dietary modifications. Nutrition played an important part in the treatment of cancer. If a patient was to receive therapy, whether radiotherapy, chemotherapy or surgery, his nutritional state was important. In the terminal stage of the disease it was of no apparent benefit to persist with concentrated feeding programmes, provided adequate nutrients were taken to prevent the development of distressing deficiencies. Miss Turner outlined the dietary modifications used at the Peter MacCallum Clinic in Melbourne.

Rehabilitation after Cancer of the Larynx.

MR. BERNARD SHELVERTON (Tasmania) outlined the meaning of rehabilitation as applied to laryngectomized persons. He said that there were special features and problems which needed consideration. They resulted from the after effects of carcinoma of the larynx and surgery for removal. Broadly the elements of rehabilitation were psychological, economic and social. Each was dependent on the other, and good recovery depended on the efficiency of rehabilitation under those three headings. The team necessary comprised the physician, surgeon, nurse, speech therapist, social worker and social guidance worker, the patient and his family, and his employers (in the broad sense). Commencing when diagnosis was made, a general plan for preoperative attention by the therapist could be evolved with the full understanding and cooperation of the medical members of the team, to continue post-operatively when their permission was given. The approach to the patient had to be considered. Understanding of the "violence" of the nervous upset in the patient was essential. Worry about the future was an aggravating factor. It was essential to assure him that he would speak, work and take his place in society. There was also a real need for practical assistance in most cases until employment was resumed or where employment was not possible. Limitations existed in the employment field if the patient was of senior age. Employers and governments must be educated to recognize the growing social and economic problem because their interest and cooperation were necessary to solve it. Covering the whole work of rehabilitation there must be the patient's full cooperation and determination if he was to fill his rightful place in the family and in society. It was pointed out that in the field of rehabilitation valuable work was being done by the New Voice Association of Australia, particularly in Melbourne.

Cancer of the Lung.

Spread of Pulmonary Tumours.

PROFESSOR R. A. WILLIS (Great Britain) presented a paper entitled "The Incidence, Types and Modes of Spread of Pulmonary Tumours with Comments on Some Fallacies and Uncertainties". In it he drew attention to discrepancies in the reports of findings of different pathologists regarding the frequency and relationships of the several histological variants of lung carcinoma and discussed some recent studies which might help to clarify the existing confusion. He said that many recent writings assumed that pulmonary carcinoma could be easily subdivided into distinct histological types. That was unsound pathology; the named types were only main variants of the single species, bronchial carcinoma, and combinations of the several named variants of the one tumour were more common than was supposed. While certain general relationships between predominant histological types, on the one hand, and sex incidence and metastatic behaviour, on the other, could be discerned, more examination of the surgical and necropsy material was needed, and general uniformity in the use of the histological type names was to be reached before conclusions could be made. Professor Willis's paper will be published in full at a later date.

The Problem of Lung Cancer and Smoking.

DR. E. L. WYNDER (U.S.A.). discussed the problem of lung cancer and smoking. He said that proof that tobacco smoking, particularly in the form of cigarettes, was a major factor in the development of lung canrer rested primarily on epidemiological studies. Epidemiological as well as pathological, chemical and biological data were presented showing causative relationship between smoking and lung cancer with special emphasis on practical preventive measures. Dr. Wynder said that in respect of smoking and cancer it was important to be concerned with means to reduce risk among smokers who could not give up smoking. Such a reduction could be obtained through the modification of smoking habits and the use of cigarettes which yielded a greatly reduced amount of condensate and nicotine. The latter could most adequately be achieved through filtration, tobacco selection and probably use of high porosity papers. Dr. Wynder outlined efforts to reduce selectively the carcinogenic or the co-carcinogenic portions of tobacco smoke condensate, either through additives that could reduce the burning temperature or otherwise modifying the combustion, or through possible extraction of precursors.

Mass X-Ray Service.

DR. B. CLEREHAN (Victoria) considered the significance of mass X-ray surveys in relation to cancer of the lung. He discussed information which had been obtained from surveys concerning the natural history of the disease and drew attention to some of the difficulties experienced in diagnosis in mass surveys. He presented an attempt to define "early diagnosis" and discussed the criteria and value of the diagnosis.

Exfoliative Cytology in Diagnosis.

DR. STEPHEN E. WILLIAMS (New Zealand) discussed exfoliative cytology in diagnosis of cancer of the lung. After referring to the historical aspects of the subject he discussed the laboratory considerations based on an eight-year experience at Green Lane Hospital, Auckland, and presented the results from 100 proved cases of lung cancer. He showed that more than 80% of cases of lung cancer would exfoliate cells which might be recognized cytologically in either sputum or bronchial washings. He compared the relative merits of sputum and bronchial washings and demonstrated the diagnostic superiority of cytology to bronchial biopsies. Dr. Williams considered that pulmonary cytology was a reliable and effective diagnostic procedure which might be included in laboratory practice without difficulty. It was cheap and undisturbing to patients, and was a logical addition to the routine screening of patients suspected of having lung cancer. In a significant number of cases cytology would establish an early and conclusive diagnosis of malignant disease and would provide a basis for immediate definitive treatment.

Results of Treatment.

MR. C. J. OFFICER BROWN (Victoria) presented a survey of the results of treatment of cancer of the lung by surgery, radiotherapy and chemotherapy. The review related to patients who had been treated in the major Melbourne hospitals.

The Management of Inoperable Cancer of the Lung.

MR. JOHN HAYWARD (Victoria) discussed the management of inoperable cancer of the lung. He said that since, at a rough estimate, only about 1% of patients with carcinoma of the lung had operable lesions and had their lesion resected, the management of the other 99% was a matter of some importance. The impact on his family of the shattering news that the patient had an incurable disease needed careful handling, and the question when and how much to tell the patient himself required the deepest sympathy and understanding. It was the duty of the doctor to do all he could to help the patient and his family to make the necessary mental adjustments to the new situation. The medical attendant must realize that a great deal could be done to relieve suffering by drugs for pain, cough, breathlessness and insomnia. The selection of suitable drugs and of the best time to prescribe them for each patient was worthy of the doctor's best efforts. On no account must he adopt a defeatist "nothing more can be done" attitude.

Systematic Management of Inoperable Cancer of the Lung.

DR. W. P. HOLMAN (Victoria) said that there were two opposite points of view which might determine the indications for radiotherapy in patients with inoperable cancer of the lung. Especially since megavoltage equipment had vastly improved the radiotherapeutic accessibility of such lesions, some believed that after the lesions had been shown to be unsuitable for radical treatment, all patients except those in a terminal state should be irradiated. Large fields were used in an endeavour to include all the known extensions of the tumour. It was hoped that by that method any present symptoms, whatever they might be, would be relieved, that others would be prevented, and that life would be prolonged. Those taking the other view limited their objectives to the treatment of certain clear-cut symptoms and strove to avoid adding any morbidity during the remainder of the patient's life—a period which it was often impossible to estimate with useful accuracy.

Social Aspects of the Diagnosis of Inoperable Cancer of the Lung.

MISS N. FANCOURT (Victoria) presented a paper on social aspects of the diagnosis of inoperable cancer of the lung. She said that the many social problems created by illness for the patient and his family should be recognized in the early stages of his treatment, and the appropriate plans should be made with the patient for his social welfare as well as for his medical care. The social needs of the patient receiving medical care for an inoperable carcinoma of the lung were in most respects similar to the needs of other patients who were entering the stage of terminal illness. The family physician visiting the patient at home had those needs thrust upon him, but in the busy hospital out-patient department they were less in the foreground. In many instances, pressure of appointments and lack of time prevented the clinician from discussing with the patient those factors in regard to his diagnosis. The diagnosis indicated that treatment could offer little hope of regression and that the patient might expect progressive disability. Experience had shown that most people found it difficult to face the diagnosis of cancer. They feared it because they believed that it must frequently be painful and that in spite of specialized medical care the end was fatal. Probably this accounted for a certain amount of secrecy about telling the patient the diagnosis. However, the very secretiveness about the diagnosis might create additional fears and anxiety about the illness. Relatives might know the diagnosis and, in attempting to hide that fact and to keep the knowledge to themselves, they were under a strain which the patient was quick to recognize. The social aspects of the diagnosis would be loss of economic status and independence and a growing feeling of humiliation and frustration. As the patient's disability increased, there would be the need for financial assistance, transport arrangements for clinical treatment, home help, home nursing and, possibly, hospital care. The assistance that could be offered the patient might be considered under three headings: (i) provision of adequate medical care; (ii) assistance to help the patient accept environmental adjustment to meet his growing economic and dependent problems and to help with difficulties which might prevent him from accepting the medical plans; (iii) sustained support, through various stages of the disease, helping the patient and his family to adjust themselves to the increasing disability.

Management of the "Pulmonary Coin Lesion".

MR. KENNETH MORRIS (Victoria) said that the advent of radiographic surveys of the community had introduced clinicians to a new clinical problem—the presence of a discrete radiological shadow in an apparently healthy patient. Usually it was impossible to make a film diagnosis of the lesion, and the radiological characteristics should not be regarded as being indicative of any particular pathological state. It might be both misleading and of disservice to the patient to recommend repeated radiographic examinations over a period of time. Experience had shown that a large proportion of such lesions were malignant; many of the remainder were conditions which were best treated by excision. For those reasons it was recommended that, in general, the patients concerned should be subjected to thoracotomy. The results of such thoracotomies had shown that many investigational methods that were commonly used were of limited value for such patients.

Pre-Operative Assessment in Relation to the Post-Pneumonectomy State.

DR. BRYAN GANDEVIA (Victoria) read a paper entitled "Pre-Operative Assessment in Relation to the Post-Pneumonectomy State." He said that the functional assessment of the patient might be considered in two complementary phases: the assessment of respiratory disability on the one hand and the assessment of the functional aspects of the lesion on the other. The assessment of respiratory disability began with an accurate history of exercise tolerance along the lines of Fletcher's questions and continued with the evaluation of physical signs of functional significance (such as wheeze, central cyanosis, accessory muscle activity and inspiratory narrowing of the subcostal angle) as distinct from the largely redundant "classical" physical signs of emphysema. Simple single breath tests of ventilatory capacity would indicate or exclude the obstructive ventilatory defect which was by far the commonest cause of respiratory disability in the age group under consideration, and provided an index of severity sufficiently accurate to prevent major catastrophes of surgical management or to guide management during the pre-operative and post-operative phases. Estimation of the ventilatory response to exercise gave an opportunity to evaluate exercise capacity. Arterial gas studies were indicated in patients doubtfully fit enough for pneumonectomy without risk of producing a "respiratory cripple". Dr. Gandevia went on to say that the functional effect of the lesion was mainly informed guess work unless bronchospirometry was done routinely, a procedure which was not advocated. Bronchial carcinoma produced functional effects in proportion to the size of the bronchus blocked and not in proportion to the size of the mass. A discrepancy between the clinical assessment of functional loss and the expected functional loss was a cardinal indication for pulmonary function studies, including bronchospirometry if simpler tests did not reveal the cause of the discrepancy. Clinical overestimation of functional capacity was common in women, while conversely functional impairment beyond that anticipated occasionally occurred when there was a gross reduction in pulmonary artery flow on the side of a neoplastic lesion which might be quite small. Dr. Gandevia said that post-pneumonectomy functional status was directly related to pre-operative status; unless surgical complications occurred, the production of a post-operative respiratory cripple was a direct reflection on pre-operative assessment. For reasons of pulmonary mechanics, a patient with one normal lung was less than half as efficient as he was with two, a point which was not sufficiently well recognized. Over-inflation of a normal lung produced functional abnormalities differing from, and less serious than, those of idiopathic obstructive emphysema, but overinflation of an already emphysematous lung was likely to lead to considerable aggravation of disability; the reasons for those statements were discussed. Surgical measures to prevent overinflation usually produced function loss in themselves, so that resection of diseased tissue remained the most conservative surgical approach from the functional point of view. Finally, in fairness, it was pointed out that radiotherapy could also radically alter pulmonary function.

Result of Resection of Pulmonary Metastases.

MR. HOWARD BROWN (South Australia) presented the results of resection of pulmonary metastases by thoracic surgeons in Australasia. The paper included only those cases in which the primary and metastatic growths had been proven histologically and had been shown to be identical. The diagnosis of pulmonary metastases had been made either by histological examination of the resected specimen and the discovery later of a similar malignant lesion elsewhere, or by the radiological demonstration and later resection of the pulmonary mass in a patient known to be suffering from an extrapulmonary malignant lesion. Mr. Brown discussed some histological difficulties in identifying the nature of pulmonary masses and also presented the indications for surgical resection of pulmonary metastases. He said that it would appear from the series presented that resection of pulmonary metastases from tumours of the kidney and colon and from some sarcomas gave the best results.

Leukæmia.

Clinical Problems of Leukæmia.

PROFESSOR H. N. ROBSON (South Australia) said that the clinical course in the majority of cases of leukæmia conformed to a fairly standard pattern, according to the type and acuity of the process. However, a number of variations occurred which were worthy of study. He then reviewed and illustrated the acute phases and the acute terminations of chronic leukæmia, the polycythæmic phases of chronic myeloid leukæmia and the thrombocythæmic syndromes. He suggested that consideration of those variant

states was of value in revealing the pleomorphic nature of some forms of leukæmia and the existence of separate factors affecting the proliferative process on the one hand and the marrow output control on the other. Closer study of those aberrant forms might prove rewarding in suggesting further lines of investigation in human leukæmia.

The Age Incidence of Leukæmia.

DR. E. V. KEOGH (Victoria) compared and contrasted the age incidences of the main forms of leukæmia with those of the common communicable diseases and certain other conditions proved to be of infectious origin. He said that the age incidences in childhood and adolescence of acute lymphatic leukæmia and of the acute infections were very similar. The combined age incidence curve for acute or chronic lymphatic leukæmia showed interesting agreements with and divergences from those of tuberculosis and infectious mononucleosis. The age incidence of myeloid leukæmia showed a different pattern. Dr. Keogh discussed possible implications of these findings.

Organization of Clinical Trials in Leukæmia.

DR. D. A. G. GALTON (Great Britain) discussed the organization of clinical trials in leukæmia and the comparative evaluation of clinical agents. He said that the conduct of clinical trials was necessarily determined in part by geographical considerations, on which depended the frequency with which patients treated on an out-patient basis could attend the clinic, and the frequency with which participants in the trial could meet to discuss the progress of the trial and any modifications which might be required in its conduct. His account would be based on experience gained in England, where a therapeutic trial in leukæmia was in progress under the auspices of the Medical Research Council, the chairman being Professor L. J. Witts. He went on to say that the objects of the trial must be clearly defined in the form suitable for statistical analysis. The number of patients required must be worked out, and from that the number of cooperating centres. Record forms were designed, and a scheme was proposed for insuring the random allocation of patients to the various dose schedules. Sources of bias in admitting patients to the trial must be recognized, even when they could not be allowed for. Dr. Galton mentioned various difficulties encountered during the conduct of a trial.

Leukæmogenesis.

DR. JACOB FURTH (U.S.A.) discussed leukæmogenesis. He said that many agents were known to be capable of producing leukæmia in laboratory animals. Little was known about the causes of spontaneous leukæmia in animals and almost nothing about those in man. Older views on the role and nature of genetic and non-genetic factors in producing leukæmia were undergoing drastic revision. The somatic mutation theory which was used to explain carcinogenesis by diverse agents such as chemicals and radiations was presently being replaced by the virus theory. Theoretically leukæmia could result (*a*) from an alteration of the cell, either nuclear or cytoplasmic, affecting the replicating control of the cell or (*b*) from virus resident cells similarly interfering with that control, or (*c*) from derangement in the host's fluid-regulating forces, resulting either in sustained over-stimulation or lack of restraint of a cell type. So conceived, the common denominator of leukæmias was derangement of homœostatic control of a hæmopoietic cell. The different hæmopoietic systems behaved as independent units. The leukæmic cells, however, whatever their cause, acquired individual features, which could be perpetuated by transplantation. In the light of the points that he had made, Dr. Furth discussed recent reports on the isolation of leukæmia viruses from normal and irradiated animals, as well as the nature of those viruses, newer techniques which facilitated their discovery and identification, reports on viruses in human leukæmias, the meaning of electron micrographic virus-like particles, problems related to induction of leukæmia by radiations and other recent contributions on the ætiology and nature of leukæmias.

Lymphocyte Homœostasis in the Pathogenesis of Lymphoid Leukæmia.

DR. DONALD METCALF (Victoria) reported a study of the pathogenesis of lymphoid leukæmia in which mouse lymphoid leukæmia had been used as a model for the human diseases chronic lymphatic leukæmia and lymphosarcoma. He said that in the genetically conditioned spontaneous disease in AKR mice it was possible to study the pre-leukæmic state in its phases, since 90% of those mice ultimately developed lymphoid leukæmia. At all ages after birth, lymphoid tissues had been found to be more extensive in AKR mice than in normal mice of other strains. Lymphocyte turnover, as judged by direct mitotic counts, was also excessive in mice destined to become leukæmic later. Studies on lymphoid leukæmia induced experimentally (by radiation, gross leukæmia virus or adrenalectomy) in other strains of mice had also shown that lymphopoiesis was excessive in the pre-leukæmic state. Two of the hormonal effector mechanisms helping to produce that hyperplastic state had been identified. In the preleukæmic state the thymus produced excessive amounts of the lymphocytosis-stimulating factor, and the adrenal cortex was hypofunctional in the production of lymphocytolytic corticosteroids. Those hormonal disturbances appeared to be mediating mechanisms by which the initiating leukæmogenic agents—gene, virus, hormones or radiations—exerted their action.

Radiotherapy in Leukæmia.

DR. J. P. MADIGAN (Victoria) discussed the place of radiotherapy in the treatment of leukæmia. He presented an analysis of all cases of leukæmia referred to the Peter MacCallum Clinic from 1950 to 1959 to illustrate the survival rates for various types of leukæmia, the indications for radiotherapy and varieties of leukæmia, the contraindications to employing radiotherapy, the types of remission obtained and the choice of radiation techniques.

Chemotherapy in Leukæmia.

DR. D. A. G. GALTON (Great Britain) discussed the use of chemotherapy in leukæmia. He stressed the importance of active record keeping and went on to consider the role of intermittent and continuous therapy in chronic granulocytic and chronic lymphocytic leukæmia with due regard to the toxicity of agents in current use.

Splenectomy in Leukæmia and Allied Disorders.

DR. G. C. DE GRUCHY (Victoria) said that until recently splenectomy had been considered to be contraindicated in leukæmia and the allied conditions of myelosclerosis and malignant lymphomas because, in general, it caused no improvement and because there was a relative high morbidity and mortality. However, evidence was accumulating to indicate that in selected cases with severe anæmia unresponsive to other forms of treatment, splenectomy resulted in significant improvement. Dr. de Gruchy discussed the selection of patients for and the results of splenectomy. He went on to say that the anæmia in the disorders mentioned was partly due to impairment of red cell production and partly due to hæmolysis, the relevant contributions varying from patient to patient. In some cases there were frank signs of hæmolysis, but in many they were absent—in other words, the hæmolysis was occult. Splenectomy was beneficial for patients in whom hæmolysis was the major ætiological factor for the anæmia and in whom the spleen was the main site of red cell destruction. The rate of hæmolysis was measured by estimating the rate of disappearance of ^{51}Cr from the blood, and the site of hæmolysis was determined by external counting of radioactivity over the liver, spleen and heart. Effective bone-marrow erythropoietic activity was estimated by the uptake of ^{59}Fe in the circulating red cells. Dr. de Gruchy presented the results of splenectomy in cases of lymphosarcoma, chronic lymphatic leukæmia and myelosclerosis. He said that it was of particular interest that the rate and site of hæmolysis were not related to the size of the spleen.

Leukæmia in Childhood.

DR. J. H. COLEBATCH (Victoria) said that leukæmia in childhood was almost invariably of the active type, and it differed from the acute leukæmia of adults in its vital statistics, in its clinical manifestations and course, in its blood picture, in its response to treatment and perhaps in its ætiology. It might be difficult to classify the cases of acute leukæmia into different ætiological types—lymphocytic, lymphoblastic, myeloblastic, premyeloblastic, etc.—but such a differentiation seemed to be useful at least with regard to therapy and prognosis. Patterns of therapy had been changing for the better almost every year since antifolic drugs were introduced in 1948. The benefits to the patient had correspondingly increased, and two-year survivals in comfort were no longer rarities. Apart from the bugbear of drug resistance, the major problems associated with treatment were infection, hæmorrhage and lesions in the central nervous system. Dr. Colebatch discussed the conditions outlined on the basis of experience with 150 cases, attention being directed particularly to vital statistics, to suspected ætiological factors, to progress in therapy and to central nervous system lesions.

The Nature of Acquired Drug Resistance.

PROFESSOR T. YOSHIDA (Japan) discussed the nature of acquired drug resistance. He said that a mixed transplantation of Yoshida sarcoma which was originally sensitive to "Nitromin", a cancer chemotherapeutic drug, and an ascites hepatoma, AH 7974, which was originally resistant to the same drug, was continued. After ten generations of the mixed transplanation, Yoshida sarcoma was successfully separated from the partner tumour AH 7974. It was then demonstrated that the sensitive Yoshida sercoma had acquired resistance to the drug. That remarkable fact might suggest that the acquirement of drug resistance was not simply based on a selection of resistant cells from among the tumour cell population. Professor Yoshida went on to say that a "Nitromin"-resistant strain of Yoshida sarcoma which had been established in the ordinary way (long-term application of the drug to the tumour) showed after a series of animal passages, of about thirty transplant generations, an evident reduction in its acquired drug resistance. However, that lost resistance was recovered by treating the tumour *in vitro* with the drug in high concentration. It was implied in tne experiment that the result of the in-vitro treatment was a selection of resistant cells. Professor Yoshida discussed problems of acquiring drug resistance by cancer cells, based on several other experiments *in vivo* as well as *in vitro* using ascites tumour cells.

Leukosarcoma.

DR. R. MOTTERAM (Victoria) said that it was occasionally observed that the blood of patients suffering from lymphosarcoma became "leukæmic". That had first been noted by Sternberg in 1904, and he had given the name leukosarcoma to the condition. A small proportion of patients with follicular lymphoblastoma had also been noted to show the change in the peripheral blood. Where leukosarcoma intervened, the original lymphosarcoma had special features, in that it showed aggressively infiltrating local growth into non-lymphatic tissue in addition to a generalized lymphadenopathy. Leukosarcoma was of abrupt onset, and subsequent survival was very short. The leukosarcoma cells in the circulation had morphological characters akin to the cells in the solid tumorous portions and could often be differentiated from the cells present in lymphatic leukæmia. It was therefore suggested that those features of aggressive local growth and the abrupt onset of a leukæmic state composed of cells having distinct morphological characters provided sufficient basis for the recognition of a particular variety of lymphosarcoma. The terminal "leukæmic" phase might be regarded as an additional expression of the unusually infiltrative quality of the type of lymphosarcoma concerned, and the condition was held to be distinct from lymphatic leukæmia.

Leucocyte Alkaline Phosphatase in Leukæmia.

DR. R. G. WYLLIE (Victoria) said that the amount of leucocyte alkaline phosphatase in myeloid leukæmia was reduced or within the normal range. Other types of leukæmia had normal or increased enzyme levels. He described an in-vitro method of inducing leucocyte alkaline phosphatase generation with the progress that had been made using that method to examine the mechanism of enzyme production in normal and leukæmic leucocytes. He discussed the significance of the experimental findings and described the experience gained in applying the test in the differential diagnosis of leukæmia.

Cancer of the Skin.

Skin Cancer as an Australian Problem.

DR. G. READ (Victoria) presented the results of a current survey in Victoria as part of a general discussion on skin cancer as an Australian problem. Dr. Read said that random samples of the adult population in selected centres throughout Victoria had been examined for evidence of cancerous and pre-cancerous lesions in the skin. He presented the results of a survey in relation to age, occupation, etc.

DR. G. G. CARMICHAEL (Queensland) presented the results of an ætiological study on the same problem. He said that it was fairly certain that ultra-violet radiation was responsible for the high incidence of skin cancer in Australia, and the purpose of the study had been to try to put that hypothesis on a factual basis for Queensland. In addition to statistical study of the incidence of skin cancer, ultra-violet radiation measurement apparatus had been installed in three places in Queensland. The mean incidence of patients presenting for treatment for the first time had been estimated to be increased from 382 per 100,000 per year for Brisbane (27° S.) to about 835 per 100,000 per year for Townsville (19° S.). The incidence rate for Cairns (17° S.) fell off somewhat, but the racial characteristics of the population entered into consideration for that city. Inland rates were higher than those on the coast, which was in keeping with the higher temperature of ultra-violet radiation concentration. Preliminary results were available for the ultra-violet estimations, and so far, for the three centres in which the recording was being carried out. Cloncurry (inland, 20° 38′ S.), had the highest readings, Townsville the next highest and Brisbane the lowest.

Pre-Cancerous Skin Changes Caused by Solar Radiation.

DR. V. J. MCGOVERN (New South Wales) presented a pathological study of pre-cancerous skin changes caused by solar radiation. He said that collagen degeneration of the skin arose in persons with inadequate cutaneous pigmentation from excessive exposure to solar radiation. At first there was replacement of collagen around the subpapillary plexus of the vessels by "elastosis". Gradually the power to form fibrils was lost, and at the same time the epidermis underwent atrophy. Melanocytes, however, increased their activity, and irregular pigmented areas appeared. That was the pre-malignant phase in the genesis of skin cancer of solar origin. Multiplication of melanocytes resulted in the melanotic freckle of Hutchinson, which eventually gave rise to overt malignant change. The addition of mild inflammation caused a dyskeratotic hyperplasia, the solar keratosis which was the predecessor of squamous carcinoma. Keratoacanthoma was almost invariably accompanied by inflammation and solar changes in the dermis. Many examples of basal cell carcinoma also were accompanied by solar degeneration of the dermis. Dr. McGovern presented evidence suggesting that the carcinogenic effect of solar radiation was mediated through alterations produced in the dermis.

Clinical Observations on Pre-Cancerous Skin Conditions.

DR. D. M. CLARK (Victoria) presented some clinical observations on pre-cancerous skin conditions. He said that the lesions containing nævus cells and the precursors of malignant melanoma would not be discussed. Of the alleged pre-cancerous conditions chronic actinic dermatosis was the cause of the statistically largest number of skin cancers in Australia and the world over. Despite opinions to the contrary, the vast majority of solar (senile) keratoses did not require radical treatment. Conservatism in management was the growing tendency among local dermatologists. He then discussed rarer pre-malignant dermatoses (excluding precursors of malignant melanoma) and their management. He made a plea for the prophylaxis of cancerophobia relating to the skin in view of the efficacy of modern methods of treatment.

Clinical Observations on the Inevitable Cancerous Change in Some Skin Lesions.

MR. B. K. RANK (Victoria) said that the clinician who had opportunity for observation of a disease or condition over a long period often saw the natural history of the disease in a perspective different from that of the pathologist who saw isolated static phases of disease in some particular area at a particular time. The research worker must account for some of the clinician's observations in any hypothesis he expounded. That applied nowhere more than in skin cancer, where a long or gradual process of change was clearly open to continued clinical scrutiny. In his paper he set out to draw attention to certain conditions in which the development of surface cancer might well be regarded as inevitable, conditioned only by the longevity of an individual patient for a sufficient period for a relentless if slow process to develop. Though the particular conditions cited might at first seem quite unrelated, it was of some value to question if there were any observations among them which might suggest common cause or mechanism of origin. He went on to discuss cancer developing in chronic ulceration (Marjolin's ulcer), cancer in post-radiation skin conditions, and cancer (melanoma) developing in a pigmented nævus. He said that in the first two conditions there was defect or interference with the normal healing process. In the third condition normal reactions to a local cellular proliferation broke down. In both circumstances, superficially unrelated, there was failure of a normal body reaction, the detailed mechanisms of which were still far from clear. It was possible that more light would follow on better understanding of the normal healing mechanism and of aberrations thereof than from present trends of seeking out some common ground, among precipitating factors which might well be fundamentally similar.

Carcinogenesis in Relation to Skin Cancer.

PROFESSOR I. BERENBLUM (Israel) discussed carcinogenesis in relation to skin cancer. He said that, though structurally and functionally complex, the skin was an ideal tissue for carcinogenic studies because of its superficial location permitting the early changes to be continuously observed. A distinction was drawn between "pre-canceroses" and "carcinoma-in-situ" on one hand and "preneoplasia" on the other. The first two represented diagnostic entities in relation to eventual malignancy; the other dealt with the critical transition from normality to neoplasia in terms of basic principles of tumour pathogenesis. The "preneoplastic" changes during the long latent period of carcinogenesis could not be discerned morphologically, for they occurred before the establishment of a visible growth—even before the appearance of the papilloma stage. Indirect experimental methods had therefore to be devised to unravel those early processes. Professor Berenblum gave an account of the experimental studies that led to the "two stage mechanism" of carcinogenesis, and of other recent advances in experimental skin carcinogenesis, and the results were discussed in relation to the problem of skin cancer in man. Professor Berenblum's paper will be published in full at a later date.

Molluscum Sebaceum.

MR. J. H. HESLOP (New Zealand) discussed the clinical and ætiological significance of molluscum sebaceum. He said that this condition had been well established as a clinical entity for the past 25 years. It was only during the last three years, however, that the condition had been recognized as such in the experimental animal. In his paper he described the production of lesions resembling molluscum sebaceum in rabbits, using twice weekly applications of 9,10-dimethyl-1,2-benzanthracene. He said that two main types of retrogressing tumour were seen—squamous papilloma and molluscum sebaceum—although intermediate lesions showing characteristics of both also occurred. The mode of development of molluscum sebaceum from the hair follicles was illustrated. It was suggested that the experimental molluscum sebaceum was the hair follicle analogue of the squamous papilloma. Further experimental evidence for the origin of molluscum sebaceum from hair follicles was provided by the failure to induce the lesion in rabbits after the application of carcinogen (i) to skin epilated by X rays and (ii) to epithelium which had regenerated after trauma and in which no hair follicles were present. Mr. Heslop reviewed a clinical series of 1500 consecutive skin tumours in the light of the experimental findings described.

An Unusual Epithelioma in Inbred Sheep.

MR. L. C. LLOYD (New South Wales) said that observations had been made on a hitherto undescribed epithelioma of the wool-bearing portions of the body of sheep. Tumours originated in the walls of cysts, the incidence of which suggested that they were transmitted genetically. The cysts lay in the dermis and consisted of several layers of flattened epithelial cells surrounding a mass of concentrically laminated soft keratin. Grass seeds were often present in the centre of the keratin mass. Cysts did not become visible macroscopically under two years, but in old animals they might number 200 to 300. Early cases of epitheliomata exhibited infiltration of the adjacent dermis and excessive keratin production resulting in rupture to the skin surface. The keratin plugs sloughed out leaving a crater of neoplastic tissue. Metastases might occur in regional lymph nodes and lungs, but animals usually died from secondary bacterial infection before that stage was reached. Epitheliomatous changes in the cyst walls could be induced by injection of 9,10-dimethyl-1,2-benzanthracene into the cysts.

Melanoma: The Liaison between Pathologist and Surgeon.

DR. J. D. HICKS (Victoria) said that the histological criteria of malignancy in melanomata did not differ from those in other tumours. In malignancy there was proliferation of cells and alteration of cell size, shape and staining, with enlargement, irregularity and mitosis of hyperchromatic nuclei. Melanin formation might be increased. The cells might extend upward to disrupt the epidermis and downward as sheets or cords invading the dermis. The two main features to be considered were the characteristics of the cells and their extension beyond normal limits. The application of those principles presupposed a knowledge of the normal and of variations of the normal short of malignancy. Difficulties were less likely to arise in cases with established malignant characteristics than in those in which it might be difficult to determine whether the cells had extended beyond normal bounds. The distinction between the earliest malignant change and simple activation of the functional nævus depended on the identification of malignant cells in the dermis which were clearly separated from the epidermis. An attempt had been made to assess those features of "early malignancy" and to follow Allan and Spitz in labelling as superficial malignant melanoma those examples in which invasion was confined to a narrow band immediately below the epidermis. If the extent of surgical measures was to depend on such a fine distinction, it was essential that the surgeon should know the limits within which pathologists exercised judgement and should appreciate the particular experience of individual pathologists.

Management of Carcinoma of the Skin.

DR. A. G. S. COOPER (Queensland), discussing the management of carcinoma of the skin in Queensland, referred to the high incidence of skin cancer in that State. He considered the available methods of treatment under the headings of radiotherapy, surgery, and caustics and diathermy. He said that radiotherapy of good standard provided a high lesion cure rate and, in concept, was more acceptable to the average patient, leading to earlier treatment of the condition. Surgery was the method of choice for cutaneous carcinoma in scar tissue, in atrophic or very poorly vascularized parts, on the lower extremities, and when recurrent after radiotherapy. There was little scope for the use of caustics and diathermy as a routine method of treatment. A method of radiotherapy had been in use for 16 years at the Queensland Radium Institute and was based on the conception of a minimum tumour dose as in more deeply situated tumours. Dr. Cooper described the application of that method in practice and the results obtained. He did not discuss malignant melanoma beyond pointing out that it was a relatively radioresistant lesion requiring a surgical approach for cure.

DR. C. C. J. MINTY (Victoria) presented experience in the management of carcinoma of the skin in a combined clinic. He said that for the past four years patients with skin cancer attending the Peter MacCallum Clinic had been referred to a special skin clinic to be seen by the plastic surgeon and radiotherapist in consultation. The aim was to gain further knowledge of the problems involved in diagnosis and treatment of skin cancer, to apply a uniform policy of management, and to investigate certain aspects, including the comparison of results of treatment by radiotherapy or surgery in selected sites, the effectiveness of X-ray therapy, the treatment of keloids and the prevention of skin cancer by means of ultra-violet filtering agents.

MR. A. R. WAKEFIELD (Victoria) said that since 1955, at the Peter MacCallum Institute, an attempt had been made to organize a combined radiotherapy and surgical consultation clinic for new cases of skin cancer in all its forms. That was instituted in order to try to determine the optimum treatment for each individual patient on a basis of cooperative and unbiased consultation between radiotherapist and surgeon. Mr. Wakefield, in his paper, attempted to define the place of surgery in the untreated lesion, in the recurrent lesion and in the management of the complications of radiation.

SCIENTIFIC EXHIBITION.

A scientific exhibition was presented in the Wilson Hall, which included 38 exhibits from individuals and institutions in Melbourne and elsewhere. The standard of presentation of the exhibits was of a particularly high order.

TELEVISION DEMONSTRATIONS.

Television demonstrations were presented by Professor M. R. Ewing and Dr. G. Berci, from the Department of Surgery, University of Melbourne, illustrating the use of television as an aid in diagnosis and its potential in postgraduate medical education.

British Medical Association.

NEW SOUTH WALES BRANCH.

Special Group of Neurology and Psychiatry.

THE annual general meeting of the Special Group of Neurology and Psychiatry of the New South Wales Branch of the British Medical Association will be held on November 3, 1960, at 6 p.m., at the Robert H. Todd Assembly Hall, British Medical Association House, 135 Macquarie Street, Sydney. After the meeting, at 7 p.m., Dr. I. Pierce James, of Perth, will read a paper entitled "Clinical and Psychological Changes Following Temporal Lobectomy". All medical practitioners are invited to attend the reading of Dr. Pierce James' paper.

Medical Societies.

MEDICAL SCIENCES CLUB OF SOUTH AUSTRALIA.

A MEETING of the Medical Sciences Club of South Australia was held on June 3, 1960, at the Medical School of the University of Adelaide, Frome Road, Adelaide.

Some Aspects of Staphylococcal Epidemiology.

DR. J. R. COULTER read a paper on staphylococcal epidemiology, in which he set the problem of staphylococcal sepsis against a short history of bacteriology. The importance of this problem was underlined in two ways. He discussed first the apparent ease with which the staphylococcus became resistant to antibiotics, and said that it was only seven years from the first reports of penicillin resistance to concern at the rising tide of that resistance. Dr. Coulter then referred to the cost of extra patient-bed days caused by post-operation wound sepsis, which was estimated at £1,000,000 annually for all Australia. Dr. Coulter then presented the results of a survey conducted among 407 mothers before, during and after their hospitalization at the Queen Victoria Maternity Hospital, together with their babies. Staphylococcal nasal carriage rates were investigated. It was shown that the carriage rate before admission to hospital was 38% with a penicillin-resistance rate of 40%. Mothers picked up few hospital strains and appeared to select sensitive ones; but in the first six weeks after discharge from hospital, they acquired hospital strains from their babies, so that at the end of that time the carriage rate was 60% and the penicillin-resistance rate 42%. Babies picked up 35% of their strains from their own mother, 36% from other mothers and 29% from the hospital staff. The baby-carrier rate on discharge from hospital was 48%, and the penicillin-resistance rate 49%. At six weeks those two figures were 55% and 50% respectively. Two-thirds of the sepsis was caused by strains present in mothers before their admission to hospital. A case was made for finding and treating carriers before hospitalization.

Out of the Past.

EPIDEMIC DISEASES.

[From "Diseases Which Should be Prevented", by James Jamieson, published by the Australian Health Society, Melbourne *circa* 1880.]

THE subject of epidemic diseases and their prevention, has so many points of contact with that of infant mortality, that they might also be considered together. I have thought it best, however, to refer to it separately, since measures for the reduction of the mortality from contagious diseases are not so completely dependent on individual knowledge and effort for their adoption, as is the case with those we have already considered. Though we are free from some of the severest forms of epidemic diseases such as small-pox, typhus, yellow fever, and cholera, yet the mortality due to maladies of that class is very great. In the five years ending 1876, the number of deaths from *measles, scarlatina, diphtheria and croup, whooping-cough, and typhoid fever,* in Melbourne and its suburbs, amounted to 3881, or rather more than 15 per cent. of the total mortality. The death-rate from these five forms of epidemics was also considerably higher than in the rest of the colony, about one-third more, this disproportion between the town and country rates being mainly caused by the excess in the death-rate from measles, scarlatina, and typhoid; the others, viz., diphtheria, including croup and whooping-cough, being about equally prevalent. Now, all these diseases are in one way or another contagious, that is to say, the poison goes from person to person, either directly or indirectly. With measles, scarlet fever, and whooping-cough, there is no room for doubt or difference of opinion, that if any person, child or adult, who has not had these diseases, comes in close contact with some one suffering from any of them, he is very sure to catch it. With diphtheria and typhoid there is not the same agreement of opinion among medical authorities, though most now believe that there is a poison given off from the body in these cases also, which may cause the same disease in healthy individuals, either directly or after a temporary lodgement in the soil or in water. This is the most important matter, that in all epidemic diseases there is a kind of poison given off by the diseased and taken up by the sound, which is the cause of the spread of these maladies from person to person, from house to house, and from town to town, in any community. There are not very many, whose opinion is of great value, who believe, that the poisons we are speaking of can arise spontaneously. Everybody believes that if small-pox is not introduced into this country from Europe or India, or some other place where it now exists, we need not be afraid that it will produce itself in some unknown way. Now, it is just the same with the epidemics already firmly rooted among us. If the people of any town, in which no cases of scarlet fever had occurred for a long time, could use the same quarantine regulations that are adopted for the purpose of preventing the introduction of small-pox into the colony by sea, there is no doubt that they might continue to be free from the scourge; or, if by chance a case was introduced, it might be prevented from spreading beyond one or two houses, as was done with small-pox in Sandhurst a few years ago.

Correspondence.

GENERAL PHARMACEUTICAL BENEFITS.

SIR: An analysis of the "Book" with a chemist friend firstly tends to give the impression that there are 927 items. This is not so. (i) There are 425 numbers missing; this leaves 502 items. (ii) Of these 502 items: 32 carry no dispensing fee; 37 high-velocity items are priced in the majority on the bulk rate; 86 have restricted use; 23 have price less than 5s. Total 178, leaving 324 items for the general public for which the full price will be paid less 5s. (iii) Of these 324 items many are duplications—e.g.: 6 numbers cover cortisone group; 4 numbers cover gas gangrene; 7 numbers cover diphtheria, diphtheria tetanus, and diphtheria tetanus and pertussis; three numbers cover dextrose injection; 5 numbers cover magnesium salts; 5 numbers cover quinine salts, and so on. (iv) Leaving less than 300 items, some of which are seldom used, and others could only be used in hospitals and are of little benefit to the patient attending doctors in private.

Yours, etc.,

Kahibah, NEWCASTLE G.P.
New South Wales.
October 7, 1960.

RISING COSTS AND MEDICAL FEES.

SIR: Dr. E. R. Roseby's letter of September 13, 1960 (MED. J. AUST., October 1, 1960), which has been quoted in the lay Press, might have been placed in its correct perspective had you seen fit to add a postscript to the effect that, as revealed by the "Medical Directory of Australia" for 1960, Dr. Roseby graduated M.B. 1900 and Ch.M. 1902, University of Sydney, and is retired from practice.

Yours, etc.,

163 North Terrace, ALAN LENDON.
Adelaide,
South Australia.
October 5, 1960.

ESCAPE FROM THE PAST.

SIR: Sir Garfield Barwick, in his Maitland lecture, derives the public demand for free hospitalization from "our origins as a penal colony". He says: "There still lingers in our minds a conception of government which is external to our community, and which, being external, owes less duties." To which it may well be replied, that now we have a government which is supposedly selected by our community, we should be able to impose on it the duties to us that we consider proper.

At this moment, when the question of the State and medical service is on the tapis, one may be pardoned for doubting if Barwick's idle fancy contributes anything to the solution of the problem. In fact, it only insults our community, which has shown by many heroic deeds that it brought from Great Britain far more than felon instincts.

If we cast our eyes over medicine in the last 150 years, we cannot but be struck by its continued change from individual to social exercise. Today the State uses this science to keep our food and water pure, to regulate our dwellings. Impelled by it, we have sewerage, control of working conditions, the combating of industrial poisoning, some prevention of pollution of the atmosphere. The State today does the main job in so far as insanity, tuberculosis, infantile paralysis, cancer and infectious disease are concerned. It builds our hospitals and in the main pays for their running costs. And, of course, there is the controversial drug scheme, medical service to pensioners and returned soldiers. It builds our medical schools and contributes greatly to their running costs, registers medical practitioners and refuses the right to practise to the innumerable varieties of charlatans. It and the municipalities maintain baby health centres and medical inspection of school-children. It sees that drugs are not counterfeited and adulterated. Urged on by the cold fact that the wealthy cannot be secure from disease if slums are allowed to maintain foci, the State even constructs houses for those who cannot afford them. The cause for this change from individual to social medicine is to be found in the vast development of industry in the last 150 years, in the consequent aggregation of the people in town, the replacement of individual concerns by huge trusts each with thousands of employees, the consequent centralization of the State and the concurrent rapid evolution of science.

If we look abroad, our experience is not unique. It is paralleled in every "free" country. In the socialist world, which we may remind Sir Garfield was not founded as a penal colony, socialization of medicine is complete and hospitalization is free. The question of free hospitalization depends purely on the actual conditions. The uneven incidence of illness pleads strongly for it—and if economic conditions pursue their usual cycle, a depression may make it compulsory for a great part of the people.

Finally, we do not lose our self-reliance if we combine to carry out social services. In any case, the people have to provide the buildings maintaining food, fuel, linen, drugs, instruments and support the staff. In the final analysis the hospital and its service represents labour by the working people. There is, therefore, no element of parasitism or departure from self-reliance in the use of a public hospital by a member of the community.

Yours, etc.,

176 Nepean Highway,
Aspendale,
Victoria.
October 3, 1960.

G. P. O'DAY.

AUSTRALIAN MEDICAL BOARD PROCEEDINGS: MEDICAL BOARD OF VICTORIA.

SIR: With reference to the statement of proceedings before the Medical Board of Victoria (MED. J. AUST., September 17, 1960), I should like it to be known that I am not the Dr. Strang referred to in the report.

Yours, etc.,

63 Collins Street,
Mebourne,
Victoria.
October 10, 1960.

RODERICK STRANG.

THE CASE FOR ABANDONING THE TRENDELENBURG POSITION IN PELVIC SURGERY.

SIR: I agree with Mr. Swain's contention that the Trendelenburg position should be abandoned in pelvic surgery, but primarily for a reason not mentioned by him.

If proper packing off of the viscera is combined with adequate retraction, then, whether or not relaxants are used, the patient may be kept in the horizontal position with advantage to all. This I have been doing for 27 years, using the Trendelenburg position only for the convenience of the perineal operator in combined abdomino-perineal resection of the rectum.

It was my good fortune to be taught by Hugh Devine, Leo Doyle and Hugh Trumble, all masters of the art of packing off the operative area in conjunction with a self-retaining retractor. Devine and Doyle used the former's detractor, while Trumble introduced the principle of malleable hands allowing of shaping to fit the problem of the moment. I use a retractor based on Trumble's original principles, and although the initial application of the hands was a little more difficult in the years prior to relaxants, once the apparatus was adjusted, it was just as effective as in cases in which relaxants are used.

My anæsthetist informs me that once I have finished packing off and applying the retractor, he is able to reduce the use of relaxants to a minimum until the abdomen is to be closed. This conflicts with Mr. Swain's statement that "Packing off the intestines presented no problem, provided the anæsthetist maintained full muscle relaxation during the whole time the abdominal cavity was open", as well as with his statement that the Trendelenburg position "was certainly necessary prior to the introduction of relaxant drugs".

Self-retaining retractors are used very rarely in capital cities in Australia, as well as abroad, probably because the surgeons in teaching hospitals are usually surrounded by hordes of clutching hands itching to get a hand inside an abdomen. These are usually best kept occupied by giving them the handle of a retractor to rest on.

I do not think that the change from using the Trendelenburg position to operating with the patient horizontal is the main explanation of the disappearance in his cases of the post-operative shock he describes as appearing fifteen minutes to two hours after an apparently satisfactory operation. I have experienced this on a number of cases in which I was reasonably sure that my operative manipulations were not responsible, and this phenomenon has occurred in this district with a number of other surgeons using varying positions of the patient and varying methods of retraction. If this type of shock occurred in the pre-relaxant days, it certainly did not attract the attention that it has of recent years.

Comment on the rest of Mr. Swain's paper I leave to the anæsthetist; but I do heartily agree with his plea for abandoning the Trendelenburg position in pelvic surgery.

Yours, etc.,

248 Latrobe Terrace,
Geelong,
Victoria.
October 10, 1960.

CHARLES GALE.

TERATOGENIC EFFECTS ON THE HUMAN FŒTUS THROUGH MATERNAL EMOTIONAL STRESS: REPORT OF A CASE.

SIR: I am surprised that in your valued journal, you can find space for such pseudo-science as that expounded in a recent issue (24/9/1960) by Dr. Elizabeth Turner. Surely the space for such stuff is the Journal of Voo-Doo, Black Magic or Astrology. It would be a matter of joking were it not for the fact that this sort of speculation percolates through to patients who then become anxious after any emotional crisis. It would not be beyond some, at an early stage of pregnancy, to say to a husband: "If you do not give me a Rolls Royce, I will have a tantrum. Then your baby will be born with its left leg missing." From this sort of reasoning we could expect the practitioners of north-central and north-western Victoria, where there has been an increase in the population of hares, since myxomatosis has reduced the rabbits, to tell us of an increase in lip and palate deformities in recent years.

Yours, etc.,

12 Collins Street,
Melbourne.
Undated.

D. F. LAWSON.

MEDICAL RESEARCH IN AUSTRALIA.

SIR: Your leading article entitled "Medical Research in Australia" and Sir Macfarlane Burnet's letter have together provoked much interest in the subject.

There is little doubt that the provision and allocation of funds for medical research are both of fundamental and equal importance. For productive investigation it must be possible for workers to plan on a long-term basis. It is essential that research work be not confined to a system of annual grants, which tends to foster the study of superficial projects which can be completed only in a race against time. Ad-hoc problems, while of some value, are in general not nearly as important contributions to fundamental knowledge as those which are investigated after planning on a

more comprehensive and unrestricted basis. Additional problems of the short-term grant include the difficulties of obtaining and training technical assistants. There is the further difficulty of guaranteeing continuity of employment to these invaluable members of a research unit. This sense of insecurity, real or unreal, which is implicit in the system of annual grants, affects not only the technical assistants, but the research worker himself. This insecurity of tenure, coupled with the vitiating effect of short-term planning, must inevitably affect the value of the work as judged by international standards.

Another facet of the problem of the allocation of funds concerns the purchase and availability of equipment of a specialized nature. While existing bodies allocate funds for the purchase of equipment, this generally becomes the property of the institution when and where the project is completed, and often is simply stored or not put to its fullest use, in spite of the fact that others in other institutions have a temporary need of the same equipment. Two immediate consequences of this situation are apparent. Firstly, the research worker attempts to find a further use for this equipment, in order to justify its expense—a most unsatisfactory state of affairs. Secondly, investigators have often to wait for very long periods to obtain funds for equipment purchase, and subsequently for its eventual delivery. A possible solution to at least a part of this major problem would require that some central body should have a large pool of selected equipment, which could be made available at short notice for people requiring it temporarily. This arrangement should hold for equipment purchased specifically from funds allocated by the central body, as well as that drawn from the equipment pool. Such a pool would do much to facilitate investigational work in Australia. It would relieve the researcher of the heavy burden of decision regarding the purchase of expensive equipment, and materially reduce the time of delivery, which in Australia can be considerable, owing to its geographical isolation. This scheme operates to some extent in Great Britain under the sponsorship of the Medical Research Council and also the British Cancer Institute. Such a plan could and should be extended to Australia. A useful extension of the equipment pool would include a maintenance branch which could store, service, recall and distribute the equipment.

The urgent need for revision of salaries for technical research assistants has been overlooked or indeed buried. A good research laboratory is enormously dependent upon its technicians, who often are of great skill and training. It is becoming progressively more difficult to gain recruits, or indeed to keep highly trained personnel from leaving research institutions, to take more remunerative appointments in industry. In our opinion this is one of the most important problems facing medical research, or indeed scientific research in Australia today. Not only must we offer a secure future to young recruits, comparable with that offered by industry, but we must do more to ensure that their training is adequate in all respects. Indeed, we should actually encourage them to seek higher qualifications.

Our considerations have thus far only considered the more financial aspects of the organization of medical research in Australia. There will indeed be many problems of a different nature to be considered. Perhaps the most important of these will be the degree of control exercised by any central body. It is essential that academic freedom in its widest sense should be preserved, and that research units should be free to pursue their own interests within the widest feasible limits possible, whatever the reason for the unit's establishment.

It has been said that the present system of research in Australia involves a wasteful reduplication of resources. Such an attitude could be disastrous. What investigator, or which unit, would choose to be entirely responsible for the future of research in fields such as cancer, atheroma or thrombosis, to the exclusion of other workers in these fields, in order to avoid this "waste"? Apart from this aspect, no two experiments are ever quite the same, and work must always be verified independently, and this latter is almost as important as the original observation. At all costs we must attempt to support individuals and small units as well as large establishments working in similar fields. Monopolies in research organization could kill the incentive which Australia has at present. Implicit in the term "wasteful" is a stultifying utilitarian attitude which should be avoided. The research organization should attempt to encourage pure as well as applied science.

One must readily admit that it is not easy to ascertain what research work is in progress in the various institutions in Australia. In this respect it would be convenient to have some abbreviated reports collected, published and circulated rapidly each year. But this can hardly be considered as a vital adjunct to research, as workers should personally accept the responsibility of keeping abreast with the current scientific literature.

In summary, we consider that the following points should be considered by any committee investigating the needs of medical research in Australia: (i) the substitution of long-term grants for the present annual ones; (ii) the establishment of a central equipment pool; (iii) the revision of conditions, training and salaries for technical assistants; (iv) the preservation of academic freedom in medical research; (v) the avoidance of monopolies in research; (vi) the discouragement of purely utilitarian attitudes.

There are many details and exceptions which have not been discussed; but we consider that the foregoing considerations are very pertinent to the future of medical research in Australia. We feel that, as it expands, its cost in the early years will not be commensurate with its productivity, and that much seemingly needless expenditure will be necessary. It is hoped that this will be met by generous and unrestricted federal and private assistance, so that funds can be readily available beyond the apparent immediate requirements.

Yours, etc.,

C. J. SCHWARTZ,
J. R. CASLEY-SMITH.

Department of the Regius Professor of Medicine,
Radcliffe Infirmary,
Oxford,
England.

October 7, 1960.

ON THE INCIDENCE OF TUBERCULOSIS IN VICTORIA.

SIR: Dr. W. Bolliger is to be congratulated for his article "On the Incidence of Tuberculosis in Victoria" (MED. J. AUST., October 1, 1960), and for drawing attention to a disease which, according to the statistics of notifiable infectious diseases published weekly in your Journal, is the second most prevalent infectious disease in Australia, being headed only by infective hepatitis, and is certainly the most important infectious disease in Australia today.

His article is complementary to your leading article of August 6, 1960, where you rightly point out the belief, so widely held, that tuberculosis is "all over bar the shouting" is far from the truth; Dr. Bolliger has shown the progress that has been made and given a good picture of the problem as we see it today. Elsewhere in your leading article you refer to the opinion of the World Health Organization experts that tuberculosis will not be eliminated as a public health problem until the prevalence of natural tuberculin reactors in children aged 14 years is reduced to less than 1%. Dr. Bolliger has shown that the figure at present is about 6%—still a long way from the goal.

Dr. Bolliger also admirably demonstrates that tuberculosis today is an eminently treatable disease, for the death rate is now down to an almost irreducible minimum, most deaths being in patients dying from some other cause "with tuberculosis" rather than "from tuberculosis".

It is of interest to compare the 862 notified cases of tuberculosis in Victoria for 1959 with 640 notified cases of cancer of the breast and 349 of cancer of the lung from figures supplied by the Anti-Cancer Council of Victoria. Perhaps Dr. Bolliger's article will cause the general practitioner and the consultant who would consider himself negligent if he missed a carcinoma of the breast to pause and ask himself of the patient who has some general symptoms and perhaps a cough, "could this patient have tuberculosis?", as for every three patients with breast cancer he will see four with tuberculosis. When cancer of the lung is added to the diseases which should be diagnosed following an abnormal chest X-ray, the figures become even more significant.

Considering all these facts, it is not surprising, but nevertheless tragic, that 30% of new cases of tuberculosis notified for 1959 have far advanced disease. In my own unit during the past few months we have had several patients who have told us that for many months prior to diagnosis they had been begging their own doctors to have their chests X-rayed, and been fobbed off with such answers as

"you couldn't have tuberculosis" and "there is no tuberculosis now"—opinions which are obviously widely, but very erroneously, held in both the medical profession and the public in general.

It is regrettable that the fear of the hazards of radiation has kept many away from mass survey X-ray and from seeking radiological examination through other channels; but it should be pointed out that the amount of radiation involved in a properly taken chest film is infinitesimal, the slogan should be: "It is safer to have a chest X-ray than to avoid it."

Finally, I would like to emphasize the value of the tuberculin test as a case-finding weapon. A positive tuberculin test means infection with tuberculosis—active or quiescent, but if quiescent the danger of later activity must never be forgotten.

Yours, etc.,

P. R. BULL,
Medical Officer in Charge,
Thoracic Unit.

Austin Hospital,
Heidelberg,
Victoria.
October 11, 1960.

USE OF "XYLOCAINE" IN POST-PROSTATECTOMY CASES.

SIR: Prostatectomy is invariably carried out on "poor risk" patients who are particularly prone to post-operative chest infections. Analgesics in the form of pethidine or morphine are the rule post-operatively to relieve pain and to curb any tendency on the patient's part to interfere with dressings and catheters. These pain-killers by respiratory depression increase the risk of chest infections.

In the Burnie General Hospital, it has been found that continuous bladder irrigation with a solution of 0·25% acetic acid containing 1 gramme per litre of "Xylocaine", run in slowly, is extremely effective in relieving post-prostatectomy pain, thus obviating the need for the more potent analgesics. The action of the "Xylocaine" is presumably that of a local anæsthetic. Not enough is absorbed into the blood-stream to cause any untoward side effects, and what little there is tends to create mild euphoria. The rate of the drip and concentration of "Xylocaine" can, of course, be adjusted to suit the individual requirements.

Not enough cases have been treated as yet for a controlled experiment to be carried out, but the impression at present is that the above therapy at least decreases morbidity, if not mortality.

I should like to thank Dr. J. Taylor, anæsthetist, who introduced the treatment, and Mr. H. D. O'Brien, Surgical Superintendent, Burnie General Hospital, for allowing me to publish this article.

Yours, etc.,

JAMES MCG. IMRAY.[1]

Royal Hobart Hospital,
Hobart,
Tasmania.
Undated.

Post-Graduate Work.

THE POST-GRADUATE COMMITTEE IN MEDICINE IN THE UNIVERSITY OF SYDNEY.

COUNTRY CONFERENCES.

THE Post-Graduate Committee in Medicine in the University of Sydney announces that the following post-graduate week-end country conferences will be held.

Conference in Surgery at Newcastle.

In conjunction with the Central Northern Medical Association, a week-end conference on surgery will be held in Room 35s, the Technical College, Maitland Road, Islington, Newcastle, on Saturday and Sunday, October 29 and 30. The programme is as follows:

Saturday, October 29: 2.15 p.m., registration; 2.30 p.m., "Investigation and Assessment of the Ischæmic Limb" (with short film), Professor J. Loewenthal and Mr. Douglas Mackenzie; 3.50 p.m., "The Treatment and Management of the Ischæmic Limb", Professor J. Loewenthal and Mr. Douglas Mackenzie.

Sunday, October 30: 10 a.m., "The Management of Peptic Ulceration and Hæmatemesis", Professor J. Loewenthal and Associate Professor G. W. Milton; 11.20 a.m., "Recent Trends in Treatment of Peptic Ulceration, including Gastro-Enterostomy and Vagotomy", Professor J. Loewenthal, Associate Professor G. W. Milton and Dr. R. S. Gye.

The combined fee for attendance is £3 3s., or £1 1s. for each section. Those wishing to attend are requested to notify Dr. R. V. Dan, Honorary Secretary, Central Northern Medical Association, 17 Bolton Street, Newcastle, as soon as possible. Telephone: Newcastle B 2244.

Conference at Albury.

In conjunction with the Border Medical Association, a week-end conference will be held at the Albury Base Hospital on Saturday and Sunday, November 19 and 20. The lecturers taking part in this conference will be the Professor of Medicine and the Professor of Surgery at the University of New South Wales, and the programme is as follows:

Saturday, November 19: 2 p.m., registration; 2.30 p.m., "Diagnosis and Management of Thyroid Disease", Professor F. F. Rundle; 4 p.m., "Coronary Artery Disease", Professor R. B. Blacket.

Sunday, November 20: 10 a.m., "Some Recent Studies in Cancer", Professor F. F. Rundle; 11.30 a.m., "Valvular Disease", Professor R. B. Blacket.

The fee for attendance at this course is £3 3s., and those wishing to attend are requested to notify Dr. H. N. Meers, Honorary Secretary, Border Medical Association, 1080 Waugh Road, North Albury. Telephone: Albury J 56.

ROYAL PRINCE ALFRED HOSPITAL: EAR, NOSE AND THROAT DEPARTMENT.

Seminar Programme, 1960: Alteration.

THE ear, nose and throat seminar at the Royal Prince Alfred Hospital, Sydney, planned for Saturday, November 12, 1960, has been cancelled. Dr. G. C. Halliday, who was to have given this seminar, will give it instead on Saturday, December 10. The title of the seminar has been changed to "Surgery of the Stapes".

THE MELBOURNE MEDICAL POST-GRADUATE COMMITTEE.

SUMMARY OF COURSES TO BE CONDUCTED IN MELBOURNE IN 1961.

THE following schedule has been drawn up as a guide for those who may be planning post-graduate study in Melbourne in 1961.

Courses for Higher Qualifications.

Part I.

The following courses are suitable for candidates for Part I of the M.D., M.S., M.G.O., D.O., D.L.O., D.P.M., D.D.R., D.T.R., D.A., Primary F.R.A.C.S., Primary F.F.A.R.A.C.S., and Part I of the Diplomas of the College of Radiologists:

Anatomy.—The course commences on February 13, and is conducted on Monday and Wednesday afternoons till August.

Physiology.—The course commences on February 27, and is arranged similarly to that in anatomy.

Pathology.—The course commences on March 6, and is conducted on Monday and Wednesday afternoons for four months. The course in pathology for F.R.A.C.S. and F.F.A.R.A.C.S. begins in late June and continues for six weeks.

Microbiology.—The course commences on April 4 and is conducted on Tuesday afternoons for twenty weeks.

Physics.—The course in physics for radiodiagnosis commences on March 16 and is conducted on Thursday afternoons for eighteen weeks. The course in physics for radiotherapy is conducted at times arranged when sufficient candidates present.

Psychology I.—This course, conducted by the University of Melbourne, will commence in mid-March and continue, five hours per week, till late October.

[1] Formerly of Burnie General Hospital.

Coaching Course in Anatomy, Physiology and Pathology.—This course for the Primary Fellowship will be conducted from January 16, full-time for six weeks, for candidates who have already studied extensively, either by attendance at courses or privately. The 1960 class is already filled.

Note.—Candidates are advised to undertake preliminary reading before commencing any of the Part I courses. The Committee conducts all the above-mentioned courses, except that in psychology.

Part II.

For senior medical qualifications, such as M.D. or M.R.A.C.P., the honorary medical staff at the Alfred Hospital will conduct a course in medicine, commencing probably in June and continuing for six or eight weeks.

For senior surgical qualifications, such as M.S. or F.R.A.C.S., the Royal Australasian College of Surgeons, Victorian State Committee, will conduct a course in surgery, full-time for ten weeks, five afternoons per week, commencing probably on August 7.

A basic course in microbiology, suitable for candidates for the M.S. and M.G.O. and the diplomas, will commence on April 4 and continue on Tuesday afternoons for about twenty weeks.

A basic course in pathology, suitable for the above-mentioned candidates will commence on March 6 and continue on Monday and Wednesday afternoons for four months.

For candidates for the D.P.M., the Australasian Association of Psychiatrists and the Mental Hygiene Authority will conduct part-time courses in psychiatry and neuropathology, commencing on March 14 and continuing in evening lectures during several months. The University of Melbourne will conduct a course in psychopathology, part-time for eight months, from March 13.

For candidates for the D.O., the Ophthalmological Society of Australia (Victorian Division) will conduct 80 lectures in ophthalmology and special pathology, chiefly in the late afternoon, commencing on April 10.

For D.A. and F.F.A.R.A.C.S. candidates, the Victorian Division of the Faculty of Anæsthetists, Royal Australasian College of Surgeons, will conduct training in the theory and practice of anæsthetics in a two weeks intensive course commencing probably in July and in two series of weekly evening tutorials, one in the autumn and one in the spring.

The following courses will be conducted at times arranged when sufficient candidates present, and those interested should get into touch with the Post-Graduate Committee without delay: (i) A course in radiodiagnosis and special pathology, to be conducted by the College of Radiologists of Australasia; (ii) a course in laryngology, otology and pathology, to be conducted by the Victorian Division of the Australian Oto-Laryngological Society. The College of Radiologists will give guidance in arrangement of study in radiotherapy and relevant pathology, and the Victorian Committee of the Royal College of Obstetricians and Gynæcologists and the University of Melbourne Obstetrics Department will advise on study in gynæcology, obstetrics and special pathology.

Refresher Courses.

A refresher course in gynæcology and obstetrics for recent graduates will commence at the Royal Women's Hospital on January 30 and continue full-time for two weeks. Residence will be available.

A refresher course in gynæcology and obstetrics for general practitioners will be conducted at the Royal Women's Hospital for two weeks, full-time, from September 11. Residence will be available.

Medical and surgical refresher courses for general practitioners will be conducted for two periods of one week each, the first in the autumn at the Royal Melbourne Hospital, the second, commencing on August 28 at Prince Henry's Hospital.

The senior medical staff of the Royal Children's Hospital will conduct a pædiatric post-graduate week from September 4.

ENROLMENT.

Commencement of courses depends on receipt of a satisfactory number of enrolments, the closing date in each case being two weeks before the date stated for commencement. Inquiries regarding all courses should be made through the conducting body, or may be addressed to the Melbourne Medical Post-Graduate Committee. The address of the Melbourne Post-Graduate Committee is 394 Albert Street, East Melbourne, C.2. Telephone: FB 2547.

The Royal Australasian College of Physicians.

EXAMINATION RESULTS.

THE following candidates, who were successful at an examination held in Australia, were admitted to Membership of The Royal Australasian College of Physicians on October 10, 1960: Dr. J. S. Duke, Dr. M. T. Havyatt, Dr. I. J. Mackie, Dr. F. L. Rothwell and Dr. G. S. Walker of New South Wales; Dr. J. K. Dawborn, Dr. J. E. Gault and Dr. B. C. Ritchie of Victoria; Dr. A. G. Collins, Dr. R. L. Hodge, Dr. D. A. Kennedy and Dr. T. A. White of South Australia; Dr. J. E. Edwards, Dr. John Ferguson and Dr. E. D. O'Callaghan of Queensland; and Dr. D. H. Gutteridge of Western Australia.

The College of Radiologists of Australasia.

RESULTS OF EXAMINATIONS FOR MEMBERSHIP.

THE names of the successful candidates in Part II of the examinations for membership of the College of Radiologists of Australasia, held in August, 1960, are as follow:

In radiodiagnosis: Dr. J. G. Barrett and Dr. F. G. Harrison, New South Wales; Dr. B. Fitzgerald, Queensland; Dr. I. C. Goy, Dr. H. W. Hardy and Dr. F. G. Warden, Victoria.
In radiotherapy: Dr. B. W. McEwen, New South Wales.

Australian College of General Practitioners.

QUEENSLAND FACULTY.

THE annual general meeting of the Queensland Faculty of the Australian College of General Practitioners was held on September 1, 1960. The following are the office-bearers of the faculty for the year 1960-1961: *Provost*: Dr. L. A. Little. *Chairman*: Dr. Robert Miller. *Vice-Chairman*: Dr. B. N. Adsett. *Honorary Secretary*: Dr. W. J. Hamilton. *Honorary Treasurer*: Dr. A. J. Parer. *Secretary*: Mr. Robert Spence. The following are the chairmen of committees: Post-Graduate, Dr. S. A. McDonnell; Medical Education, Dr. E. N. Cheesman; Publications, Dr. B. C. Harvey; Research, Dr. H. S. Patterson; Preventive Medicine, Dr. H. S. Patterson.

University Intelligence.

UNIVERSITY OF SYDNEY.

Medical Research Fellowships.

APPLICATIONS are invited for the following medical research fellowships of the University of Sydney for the year 1961: Reginald Maney Lake Scholarship and Amy Laura Bonamy Scholarship for pathological research; Anderson Stuart Memorial Research Fellowship, Marion Clare Reddall Scholarship and Joseph Goodburn-Smith Scholarship for research in any branch of medical science; Liston Wilson Fellowship for research in spastic paralysis or some closely allied subject; Norman Haire Fellowship for research in sexology, continuing and expanding work the nature of which is already being done in the Faculty of Medicine; Phyllis Anderson Research Fellowship for research in any branch of medical science; Sister Sanders Scholarship for part-time research into some aspect of the diseases of children, with particular reference to the preventive aspect.

Fellowships are renewable for a second and, in certain circumstances, for a third year. All fall due on January 1, 1961. All are to the value of £1800 or £2200 *per annum* according to qualifications and experience except the Phyllis Anderson Research Fellowship, which is to the value of £1800 or £2500 *per annum*, and the Sister Sanders Scholarship, which is to the value of £540 *per annum*.

Applications for fellowships for 1961 should be made to the Registrar, and will close on November 25, 1960. The fellowships for 1961 will be awarded in December, 1960. Application forms may be obtained from the Registrar's office. Details of these fellowships (excluding the Phyllis Anderson Research Fellowship, concerning which information may be obtained from the Registrar) are given in the "Calendar of the University of Sydney" for 1960, at pages 530 to 534.

Notes and News.

Nobel Prize Award to Sir Macfarlane Burnet.

It has been announced that the 1960 Nobel Prize for Medicine has been awarded jointly to Sir Macfarlane Burnet, Director of the Walter and Eliza Hall Institute of Medical Research, Melbourne, and Professor P. B. Medawar, Jodrell Professor of Zoology and Comparative Anatomy in the University of London.

Auxiliary Health Personnel.

The need for auxiliary health personnel is increasingly acute both in the less-developed countries where fully-trained doctors are scarce, and in developed areas where the contrary is true. The more specialized medicine becomes, the more jobs the doctor can, and should, pass on to someone else, especially essential laboratory and other technical procedures. This was underlined at a recent meeting of a World Health Organization Expert Committee on Professional and Technical Education of Medical and Auxiliary Personnel, attended by specialists from eight countries. It was pointed out, for example, that there were more than 29,000 auxiliary health workers in the U.S. Veterans Administration alone. Moreover, in the U.S.S.R., which is one of the countries of the world best supplied with doctors in proportion to population, there is still a substantial demand for medium grade health staff with fewer years of preparation. The training and employment of doctors and other professional personnel is so expensive that it is considered uneconomical for them to spend their time on tasks that can be done by skilled assistants. On the other hand, all classes of health workers are lacking in many countries, and auxiliaries must undertake great responsibilities until enough professional personnel can be trained. The Expert Committee outlined the best methods of preparing these auxiliaries for their work, especially medical assistants, auxiliary nurses, midwives and sanatorians. A distinction was made between multi-purpose and single-purpose workers, an example of the latter being sprayers in malaria eradication teams, who are required to perform a relatively simple task for a limited time. It was considered better, whenever possible, to give broader training than this, with a good deal of emphasis on public health, so that auxiliaries could be rapidly adapted to other posts when required.

Carbromal and Bromvaletone Declared Poisons in A.C.T.

An announcement by the Commonwealth Minister for Health in the *Commonwealth of Australia Gazette*, No. 68, of October 13, 1960, declares carbromal and bromvaletone to be poisons for the purposes of the Poisons and Dangerous Drugs Ordinance, 1933-1954. This is effective within the Australian Capital Territory.

Retirement of Dr. Hilary Roche.

The Commonwealth Minister for Health, Dr. D. A. Cameron, has announced that Dr. Hilary Roche, who has directed the Commonwealth-wide campaign against tuberculosis since July, 1957, will retire in December. Dr. Roche was appointed Director of Tuberculosis in 1957, after the voluntary retirement of Sir Harry Wunderly. Dr. Roche became Assistant Director of Tuberculosis in 1951, after having been for many years medical superintendent of the British Sanatorium at Montana, Switzerland.

Dr. Cameron paid a tribute to Dr. Roche's skill, experience and qualifications, and said that his knowledge and advice to Commonwealth departments, State Governments and the medical profession has been of great value to Australia. He had made many contributions to medical literature. In 1944,

DISEASES NOTIFIED IN EACH STATE AND TERRITORY OF AUSTRALIA FOR THE WEEK ENDED SEPTEMBER 24, 1960.[1]

Disease.	New South Wales.	Victoria.	Queensland.	South Australia.	Western Australia.	Tasmania.	Northern Territory.	Australian Capital Territory.	Australia.
Acute Rheumatism	1	2(1)	2	..	..	..	1	..	6
Amœbiasis	..	..	..	..	..	..	..	..	..
Ancylostomiasis	1	..	1	..	..	..	3	..	5
Anthrax	..	..	..	..	..	..	..	..	..
Bilharziasis	..	..	..	..	..	..	..	..	..
Brucellosis	..	..	..	..	1	..	..	..	1
Cholera	..	..	..	..	..	..	..	..	..
Chorea (St. Vitus)	..	2	..	..	..	..	..	..	2
Dengue	..	..	..	..	..	..	..	..	..
Diarrhœa (Infantile)	10(3)	13(10)	4	..	2	1(1)	6	5	41
Diphtheria	..	..	..	..	..	1(1)	..	..	1
Dysentery (Bacillary)	..	..	1	..	..	..	..	1	2
Encephalitis	..	..	..	1	..	..	..	..	1
Filariasis	..	..	..	..	..	..	..	..	..
Homologous Serum Jaundice	..	..	..	..	..	..	..	..	..
Hydatid	..	..	..	..	..	..	..	..	..
Infective Hepatitis	138(65)	72(56)	15(4)	14(4)	7(5)	2	..	4	252
Lead Poisoning	..	..	3	..	..	..	..	..	3
Leprosy	..	..	..	..	..	..	..	..	..
Leptospirosis	..	..	4(1)	..	..	..	..	..	4
Malaria	..	..	1(1)	..	..	..	..	..	1
Meningococcal Infection	2	2(1)	..	..	..	..	..	..	4
Ophthalmia	..	..	..	..	..	..	..	..	..
Ornithosis	..	..	..	..	..	..	..	..	..
Paratyphoid	..	..	..	..	..	..	..	..	..
Plague	..	..	..	..	..	..	..	..	..
Poliomyelitis	..	..	..	..	1	2(1)	..	..	3
Puerperal Fever	3	1	1	..	..	..	..	..	5
Rubella	..	18(15)	..	1	4(4)	..	..	..	23
Salmonella Infection	..	..	..	..	..	..	..	..	..
Scarlet Fever	10(6)	12(10)	7(5)	4(3)	..	1	..	..	34
Smallpox	..	..	..	..	..	..	..	..	..
Tetanus	..	..	1	..	..	..	..	..	1
Trachoma	..	..	..	..	15(1)	..	3	..	18
Trichinosis	..	..	..	..	..	..	..	..	..
Tuberculosis	64(41)	9(5)	15(1)	12(7)	5(3)	..	2	..	107
Typhoid Fever	2	1(1)	..	1(1)	..	..	1	..	5
Typhus (Flea-, Mite- and Tick-borne)	..	..	..	..	..	..	..	..	..
Typhus (Louse-borne)	..	..	..	..	..	..	..	..	..
Yellow Fever	..	..	..	..	..	..	..	..	..

[1] Figures in parentheses are those for the metropolitan area.

when he was medical superintendent of the Austin Hospital at Heidelberg, Victoria, he published in THE MEDICAL JOURNAL OF AUSTRALIA an article delineating the general principles of a campaign which he believed would control tuberculosis in Australia. This was the basis of the tuberculosis campaign when it was initiated in 1948.

Medical and Hospital Benefits.

According to figures recently released 72% of the total population of Australia is covered by medical benefits and by hospital benefits. There are 83 medical benefits organizations in Australia with a total membership of 2,907,671. The percentage of the population covered in the individual States for medical benefits is as follows: N.S.W. 82%, Victoria 67%, Queensland 55%, South Australia 70%, Western Australia 72%, Tasmania 69%.

There are 115 hospital benefits organizations with a total membership of 2,907,990. The percentage of the population covered in the individual States by hospital benefits is as follows: N.S.W. 72%, Victoria 73%, Queensland 55%, South Australia 76%, Western Australia 79%, Tasmania 77%.

Second International Symposium on Chemotherapy.

The Second International Symposium on Chemotherapy will be held in Naples from September 14 to 17, 1961. Professor L. Donatelli and Professor F. Magrassi will preside. The subjects of this Congress are as follow: new antibiotics, chemotherapy of virus infections, chemotherapy of cancer, secondary effects of modern chemotherapy, chemoprophylaxis and chemotherapy of atomic radiations, etc. Further information may be obtained from the Secretary of the Congress, Professor P. Preziosi, at the following address: Casella postale 266, Napoli, Italia.

Nominations and Elections.

THE undermentioned has applied for election as a member of the New South Wales Branch of the British Medical Association:

Halmagyi, Alice Julia, M.D. (Univ. Szeged), Reg. Section 17 2A, 24 Churchill Crescent, Cammeray.

The undermentioned have been elected as members of the New South Wales Branch of the British Medical Association: Arter, Warren James, M.B., B.S., 1960 (Univ. Sydney); Henderson-Smart, Arthur MacCubbin, M.B., B.Ch. 1947 (Univ. Witwatersrand); Hidi, Madelaine, M.D., 1953 (Univ. Budapest), licensed under Section 21 c (4), *Medical Practitioners Act*, 1938-1958; Joseph, Cappil Philip, M.B., B.S., 1959 (Univ. Sydney); O'Sullivan, Peter Robert, M.B., B.S., 1958 (Univ. Sydney); Papp, Peter, M.D., 1955 (Univ. Pecs), licensed under Section 21c (4), *Medical Practitioners Act*, 1938-1958; Shearer, Alex Michael, M.B., B.S., 1959 (Univ. Sydney); Stewart, Frederick Harold, M.B., B.S., 1959 (Univ. Sydney); Tester, Malcolm Percy, M.B., B.S., 1960 (Univ. Sydney); Thomson, Brian Ferguson, M.B., B.S., 1960 (Univ. Sydney); Walsh, Thomas, M.B., B.Ch., 1950 (N.U. Ireland); Wong-See, Jenson Junn-Sing, M.B., B.S., 1957 (Univ. Sydney).

The undermentioned have been elected as members of the South Australian Branch of the British Medical Association:

Barclay, Evelyn Frances, M.B., Ch.B., D.C.H., 1957; Rozenbilds, Jeff Girts, M.B., B.S., 1959 (Univ. Adelaide); Bailie, James Gibson, L.R.C.P.I., L.R.C.S.I., 1958; Coulter, Carol Gladys Roberta, L.R.C.P.I., L.R.C.S.I., 1958.

Deaths.

THE following deaths have been announced:

AHERN.—Edward Denis Ahern, on October 11, 1960, at Brisbane.

CARVOSSO.—Arthur Benjamin Carvosso, on October 11, 1960, at Brisbane.

MACDONALD.—Alan John Macdonald, on October 16, 1960, at Melbourne.

PELL.—John William Pell, on October 15, 1960, at Bunbury, Western Australia.

Diary for the Month.

OCTOBER 29.—New South Wales Branch, B.M.A.: Branch Meeting.
NOVEMBER 1.—New South Wales Branch, B.M.A.: Organization and Science Committee.
NOVEMBER 2.—Western Australian Branch, B.M.A.: Branch Council Meeting.
NOVEMBER 3.—South Australian Branch, B.M.A.: Council Meeting.
NOVEMBER 4.—Queensland Branch, B.M.A.: Clinical Meeting in conjunction with Mater Misericordiæ Hospital Clinical Society.
NOVEMBER 8.—New South Wales Branch, B.M.A.: Executive and Finance Committee.
NOVEMBER 9.—Victorian Branch, B.M.A.: Branch Meeting.
NOVEMBER 10.—New South Wales Branch, B.M.A.: Public Relations Committee.
NOVEMBER 11.—Queensland Branch, B.M.A.: Council Meeting.
NOVEMBER 11.—Tasmanian Branch, B.M.A.: Branch Council.

Medical Appointments: Important Notice.

MEDICAL PRACTITIONERS are requested not to apply for any appointment mentioned below without having first communicated with the Honorary Secretary of the Branch concerned, or with the Medical Secretary of the British Medical Association, Tavistock Square, London, W.C.1.

New South Wales Branch (Medical Secretary, 135 Macquarie Street, Sydney): All contract practice appointments in New South Wales.

South Australian Branch (Honorary Secretary, 80 Brougham Place, North Adelaide): All contract practice appointments in South Australia.

Editorial Notices.

ALL articles submitted for publication in this Journal should be typed with double or treble spacing. Carbon copies should not be sent. Authors are requested to avoid the use of abbreviations, other than those normally used by the Journal, and not to underline either words or phrases.

Authors of papers are asked to state for inclusion in the title their principal qualifications as well as their relevant appointment and/or the unit, hospital or department from which the paper comes.

References to articles and books should be carefully checked. In a reference to an article in a journal the following information should be given: surname of author, initials of author, year, full title of article, name of journal, volume, number of first page of article. In a reference to a book the following information should be given: surname of author, initials of author, year of publication, full title of book, publisher, place of publication, page number (where relevant). The abbreviations used for the titles of journals are those of the list known as "World Medical Periodicals" (published by the World Medical Association). If a reference is made to an abstract of a paper, the name of the original journal, together with that of the journal in which the abstract has appeared, should be given with full data in each instance.

Authors submitting illustrations are asked, if possible, to provide the originals (not photographic copies) of line drawings, graphs and diagrams, and prints from the original negatives of photomicrographs. Authors who are not accustomed to preparing drawings or photographic prints for reproduction are invited to seek the advice of the Editor.

Original articles forwarded for publication are understood to be offered to THE MEDICAL JOURNAL OF AUSTRALIA alone, unless the contrary is stated.

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